ETOP 12-17 ALERT-lung

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

ALERT-lung: ALEctinib for the treatment of pretreated RET-rearranged advanced non-small cell lung cancer

Sponsor and Coordinating Group:

European Thoracic Oncology Platform (ETOP)

Collaborative Group:

Lung Cancer Group Cologne

EudraCT number: 2017-002063-17

Roche Number: MO30176

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In collaboration with F. Hoffmann-La Roche Ltd.

Protocol Signature Page

ETOP 12-17 ALERT-lung

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Approved by:

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Trial Chair

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Date

Jürgen Wolf
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Date

Anita Hiltbrunner
ETOP Director

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Date

Principal Investigator Protocol Signature Page

ETOP 12-17 ALERT-lung

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I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations. I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by ETOP, to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the trial. I agree to keep accurate records on all patient information including patient's informed consent statement, drug shipment and return forms, and all other information collected during the trial for a minimum period of 15 years.

Name of Principal Investigator: _____

Institution's name and place: _____

_____ _____

Signature Date

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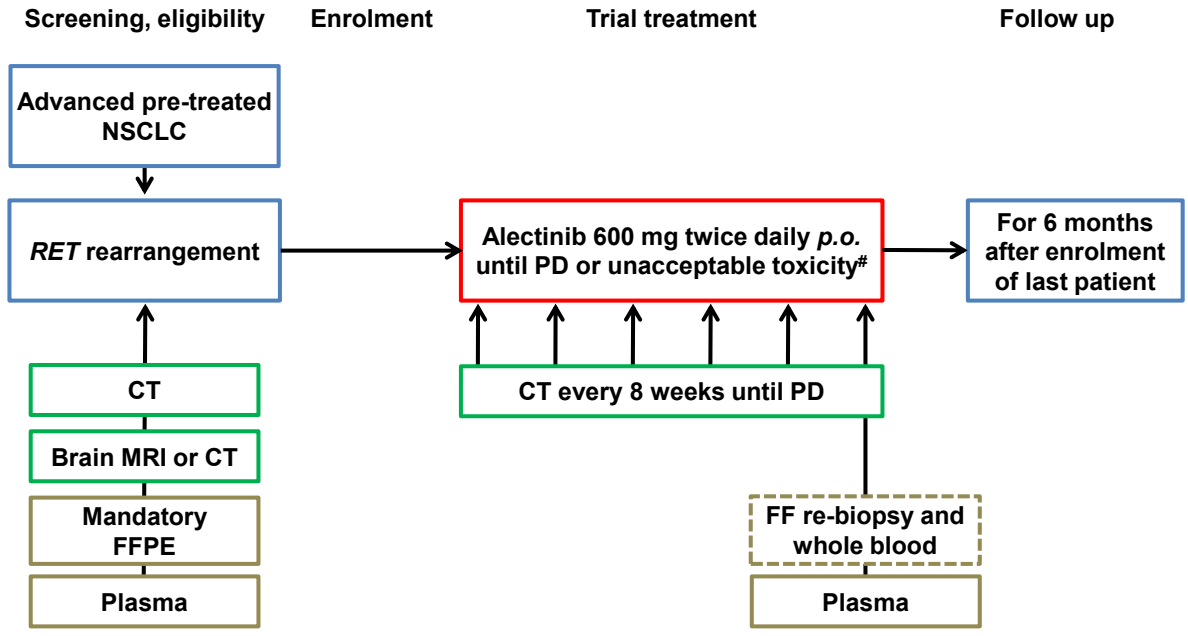
Coordinating group:	ETOP
Collaborative group:	Lung Cancer Group Cologne
Pharma Partner:	Roche
Population:	Patients with advanced stage RET-rearranged NSCLC, treated with at least one platinum based systemic chemotherapy regimen.
Design:	Single arm, phase II, multicentre trial



treatment may continue beyond progression if there is clinical benefit

Sample size: 44 patients

A total of 44 enroled patients are required and based on the low incidence of RET rearrangement in NSCLC (1-2%) approximately 4500 patients are expected to be screened in order to find enough eligible patients. The patients will be recruited from approximately 30 centres in eight different European countries.

Treatment:

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.

Treatment has to start as soon as possible after enrolment, ideally within 7 days. Treatment visits are planned at treatment start (week 0) and then every 2 weeks (±3 days) for the first 12 weeks and every 4 weeks (±3 days) thereafter.

Rationale:

Despite advances in the treatment of non-small cell lung cancer (NSCLC) over the past several decades, only small incremental overall survival benefits have been demonstrated and treatments beyond first-line remain limited in unselected NSCLC.

In 2004 the discovery of the Epidermal Growth Factor Receptor (EGFR) mutations in NSCLC and their predictive value for therapy with EGFR tyrosine kinase inhibitors (TKIs) opened the way to an intense program of research on lung cancer, aiming at identifying other genomic or protein alterations that could be used as target for treatment. Subsequently, genetic rearrangements of the anaplastic lymphoma kinase (ALK) gene in lung cancer and its oncogenic features were discovered in 2007. The impressive clinical results obtained with the inhibition of ALK and EGFR kinases compared to classical chemotherapy further supported the hypothesis that targeting signaling pathways aberrantly active in cancer cells, might lead to a better outcome of therapy for molecularly selected lung cancer patients. However, EGFR mutations and ALK translocations cover only 15-20% of NSCLC in Western populations, calling for discovery and development of novel targets. Studies on molecular alterations of lung tumours highlighted specific differences of biomarkers expression and role in the several histotypes of lung cancer. Adenocarcinoma (ADC) is the most prevalent histologic subtype among lung tumours and certainly the most characterized for its molecular features. To date, a targetable alteration may be recognized in 20-30% of adenocarcinomas in Caucasian patients.

RET fusion in NSCLC

After the discovery of ALK fusions, other genes have been to be found genetically rearranged in lung cancer. Gene fusions may occur as consequence of chromosomal translocation, inversion or interstitial deletion. Oncogenic rearrangements may cause the expression of new proteins or of a protein with different activity than the native one. Fusion can bring a gene under the control of a strong promoter, causing aberrant expression of a protein in cells where usually the protein has no or low expression.

The RET gene is located on chromosome 10 and encodes for a transmembrane receptor with tyrosine kinase activity. It is involved in cell proliferation, migration, differentiation, and in neuronal navigation. Germline and somatic mutations of RET are known to cause the multiple endocrine neoplasia type 2 (MEN2) syndrome and are involved in the tumourigenesis of sporadic medullary thyroid cancer. Furthermore, RET rearrangements are involved in sporadic and radiation induced papillary thyroid carcinoma. RET fusions are transforming in

vitro and in vivo, and inhibition of RET in RET-rearranged lung cancer cells leads to suppressed viability.[1]

RET rearrangements have been identified in lung ADC as well, with a prevalence of 1-2%.[2-4] Several genes, such as KIF5B, CCDC6, NCO4 and TRIMM33,[2,3,5] can act as fusion partners. RET-positive lung carcinomas are more common in poorly differentiated tumours and in never-smokers. Therapeutically, several multiple kinases inhibitors, such as vandetanib (Astrazeneca, London, England), cabozantinib (Exelis Inc. USA), ponatinib (Ariad, USA), axitinib (Pfizer, USA), sunitinib (Pfizer, USA), sorafenib (Bayer Healthcare, Germany), and alectinib (Roche, Switzerland) are potentially able to inhibit RET kinase function. Phase III trials data in biologically unselected NSCLC are available for some of these agents both as monotherapy and in combination. However, all the results from these studies were negative and none of the drugs was approved for lung cancer treatment, probably due to the absence of genotypic selection. On the other hand, some case reports describe anecdotal responses to treatment with vandetanib and cabozantinib in RET-positive lung cancer patients.[5-11]

Alectinib

Alectinib (RO5424802, Alecensa®) is a highly selective next generation ALK inhibitor. In preclinical in vitro enzyme inhibition assays alectinib has been shown to selectively inhibit ALK, but also RET.[12] The compound also showed high antitumour activity both in vitro and in vivo against tumour cell lines with some type of ALK gene alteration, including NSCLC and anaplastic large cell lymphoma lines harbouring an ALK translocation and a neuroblastoma line harbouring amplified ALK gene.[12]

The clinical development program for alectinib, comprises several phase I-III studies in patients with ALK-positive NSCLC:[13]

Two phase I/II studies (NP28761/AF-002JG and NP28673) evaluating alectinib in crizotinib-failed ALK-positive NSCLC patients are being conducted in North America, Europe, and other countries. One hundred and thirty four patients are enroled in study NP28761 (data cut-off date: 22 January 2016) and 149 patients are enroled in study NP28673 (data cut-off date: 01 February 2016), both of which are ongoing.[14]

The first in human phase I/II study in ALK-positive crizotinib-naïve NSCLC, AF-001JP, is being conducted in Japan. The AF-001JP study is ongoing, with 70 patients enroled. Study WP29158 is a phase 1b study of the safety and pharmacology of atezolizumab administered with erlotinib or alectinib in patients with advanced NSCLC.[15]

Clinical pharmacology studies have also been conducted in healthy subjects and patients. A study (NP29783) to evaluate the pharmacokinetics of alectinib in subjects with moderate to severe hepatic impairment is currently ongoing.

The global phase III study (BO28984) to evaluate alectinib versus crizotinib in patients with treatment-naïve advanced ALK-positive NSCLC is ongoing. A separate phase III study (JO28928) with a design similar to the BO28984 study in patients with ALK-positive NSCLC who are treatment-naïve or have received one line of standard chemotherapy is ongoing in Japan.

A phase III study (MO29750) was started in October 2015 to evaluate alectinib versus pemetrexed or docetaxel in patients with ALK-positive advanced NSCLC, previously treated with platinum-based chemotherapy and crizotinib.

A phase III study (YO29449) was started in June 2016 to evaluate the efficacy and safety of alectinib versus crizotinib and to evaluate the pharmacokinetics of alectinib in Asian participants with treatment-naive ALK-positive advanced NSCLC.

In addition, there is an ongoing post marketing drug use surveillance (ALC1401) study in Japan.

Alectinib for RET-rearranged NSCLC

Preclinical studies have recently shown that alectinib has potent anti-tumour activity in RET-rearranged NSCLC. In a kinase inhibitory assay, alectinib inhibited RET kinase activity with an IC50 of 4.8 nM, and in an ATP-competitive binding assay, alectinib bound to RET at a dissociation constant value of 7.6 nM. The IC50 for alectinib for RET kinase appears to be higher than for ALK kinase (1.9 nM), which may indicate a need for a higher dose of alectinib than currently approved for ALK+ NSCLC (600 mg orally twice a day) to ensure efficacious/therapeutic concentrations are achieved in this population.[12]

To date, a unique small clinical report of alectinib activity in RET-rearranged NSCLC is available. Recently, in the Journal of Thoracic Oncology, the Massachusetts General Lung Group reported on four RET-rearranged advanced NSCLC patients who were treated with alectinib (600 mg twice daily, N=3; 900 mg twice daily, N=1) as part of single-patient, compassionate use protocols or off-label use of the commercially available drug. Three of the four had received prior RET TKIs including cabozantinib and experimental RET inhibitors. In total, they describe two (50%) objective radiographic responses following treatment with alectinib (one confirmed and one unconfirmed), with durations of therapy of 6 months and 5+ months (treatment ongoing), respectively. Notably, one of these two patients was dose-escalated to alectinib 900 mg twice daily and had clinical improvement in central nervous system metastases. In addition, one patient (25%) experienced a best response of stable disease lasting ~6 weeks (drug discontinued for toxicity). A fourth patient who was RET-TKI-naïve had primary progression on alectinib. Therefore, alectinib demonstrated preliminary antitumour activity in advanced RET-rearranged NSCLC patients.[10]

Objectives and endpoints:

The primary objective is to assess the efficacy of alectinib in terms of best overall response (OR) assessed by RECIST v1.1. The secondary objectives are to evaluate secondary measures of clinical efficacy including disease control, progression-free survival (PFS), and overall survival (OS) as well as to assess safety and tolerability of the treatment and to describe the association of primary and secondary outcomes with tumour characteristics.

Primary endpoint:

Best overall response (OR = CR or PR), per investigator assessment, according to RECIST 1.1., from the start of trial treatment across all time points until the end of trial treatment.

Secondary endpoints:

- Best overall response per independent review
- Disease control at 24-weeks: best overall response of CR or PR, or SD (or non-CR/non-PD in the case of non-measurable disease only)
- Progression-free survival defined as the time from the date of enrolment until documented progression or death, if progression is not documented
- Overall survival defined as time from the date of enrolment until death from any cause
- Safety and tolerability (see Section 13.5)

Most important eligibility criteria (see Section 7 for complete list):

Inclusion criteria

- Histologically or cytologically-documented non-small cell lung carcinoma
- Advanced disease defined as recurrent stage IV (according to 8th TNM classification) or recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemo-radiation therapy for locally advanced disease)
- RET rearrangement detected by FISH, Nanostring or by parallel-sequencing on FFPE tumour tissue (biopsy, resection or cytoblock) assessed locally.
- Availability of FFPE tumour material for central confirmation of RET-rearrangement
- At least one prior platinum-based systemic regimen: Adjuvant or neoadjuvant or definitive platinum-based chemo-radiotherapy treatments are considered as a line of treatment only if completed less than 6 months before enrolment. Maintenance therapy following platinum doublet-based chemotherapy is not considered a separate regimen of therapy.
- Measurable or non-measurable, but radiologically evaluable (except for skin lesions) disease according to RECIST v1.1 criteria
- Adequate haematological, renal and liver function
- ECOG Performance Status 0-2

Exclusion criteria

- Untreated, active CNS metastases
- Carcinomatous meningitis
- Baseline symptomatic bradycardia
- Prior treatment with any RET TKI or RET targeted therapy
- Known EGFR, ALK, ROS, and BRAF mutation (in addition to RET rearrangement)
- Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post-major bowel resection
- History of hypersensitivity to any of the additives in the alectinib drug formulation
- Pregnant or lactating women
- Known HIV positivity or AIDS-related illness
- Any concurrent systemic anticancer therapy

Statistical considerations:

The trial targets a best OR rate of 35% and considers an OR rate of 15% as too low.

Based on a one-sided exact test for proportions, the trial is designed to test the following hypotheses:

H_0: $p_0 \leq 0.15$ vs H_A: $p_A > 0.35$, where p is the rate of best OR (ORR) at a one-sided significance level of 0.025 and a power of at least 0.80.

A significance level of 0.015 and power of 0.82 are achieved with a sample size of 41 evaluable patients. The null hypothesis will be rejected and the alternative hypothesis accepted if at least 12 patients achieve OR.

The total sample size of 44 patients allows for up to 3 patients to be replaced if a patient is ineligible (retrospective review), has not started the experimental treatment or is lost to follow-up before evaluation of response.

Total trial duration:

Clinical visits are expected to span approximately 44 months after enrolment of the first patient. Assuming an accrual rate of approximately 1 patients per month and a start-up period of 6 months as the trial is activated by participating centres, the final trial report is expected to be available approximately 5 years after the enrolment of the first patient.

2. List of abbreviations

ADC	Adenocarcinoma
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil count
AP	Alkaline Phosphatase
AST	Aspartate Transaminase
AUC	Area Under the Curve
BCRP	Breast Cancer Resistance Protein
CI	Confidence Interval
CNS	Central Nervous System
CPK	Creatinine Phosphokinase
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	Disease Control
DCR	Disease Control Rate
DLTs	Dose-limiting toxicities
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
EGFR	Epidermal Growth Factor Receptor
ERB	Ethical Review Board
ETOP	European Thoracic Oncology Platform
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin Fixed, Paraffin Embedded
FISH	Fluorescent In-Situ Hybridization
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IC	Informed Consent
ICH GCP	International Conference on Harmonisation’s Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
i.v.	Intra-venous
LDH	Lactate Dehydrogenase
LFU	Lost to Follow-up
MEN2	Multiple Endocrine Neoplasia Type 2
MRI	Magnetic Resonance Imaging
NE	Not Evaluable
NGS	Next Generation Sequencing
NSCLC	Non-Small Cell Lung Carcinoma
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PIS	Patient Information Sheet
PK	Pharmacokinetics
p.o.	Orally / per os
PR	Partial Response
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TKI	Tyrosine Kinase Inhibitor
TNM	Tumour, Node, Metastases
ULN	Upper Limit of Normal Lab Value
WBC	White Blood Cell Count
WC	Withdrawal of Consent
WES	Whole-Exome Sequencing

3. Trial schedule

	Baseline evaluation within 28 days prior to enrolment	**At every treatment visit**[13]		**At PD**	**End of treatment visit**[14]	**Follow-up**	
		Before PD	Beyond PD[11]			Before PD[15]	After PD[16]
Written informed consent for trial participation[1]	(within 6 weeks prior to enrolment)						
Medical history (smoking history, comorbidities, allergies)							
Patient diary							
Physical exam[2]							
Baseline symptoms[3]							
Adverse events[3]							
Survival							
Biological material, central laboratory and pathology							
FFPE block for central confirmation of RET rearragement[4]							
Plasma sample for translational research[6]							
Rebiopsy, fresh frozen[5][6]							
Whole blood for reference DNA[6]							
Laboratory tests							
Haematology: WBC, haemoglobin, platelets, neutrophils		(17)	(17)				

	Baseline evaluation within 28 days prior to enrolment	**At every treatment visit**[13]		**At PD**	**End of treatment visit**[14]	**Follow-up**	
		Before PD	Beyond PD[11]			Before PD[15]	After PD[16]
Hepatic function[7]: ALT, AST, AP, bilirubin, GGT, LDH		(7)	(7)		(7)		
Renal function: serum creatinine, calculated creatinine clearance		(17)	(17)		(17)		
Urine analysis (microscopic urine analysis or dipstick): pH, proteins, glucose, blood[8]		(17)	(17)		(17)		
Chemistry: CPK[9], sodium, potassium, calcium, magnesium, phosphate, glucose		(17)	(17)		(17)		
Pregnancy test if applicable[10]							
Treatment							
Alectinib 600 mg p.o. twice daily until PD[11]							
Concomitant medication							
Further lines of treatment							
Disease evaluation							
Electrocardiogram							
Brain MRI or contrast enhanced CT	(within 6 weeks prior to enrolment)						
CT thorax and upper abdomen[12]		Every 8 weeks (±4 days)			(18)	(19)	

Mandatory evaluations

(1) Before any trial-specific evaluations and intervention.

(2) Physical exam according to local standards, including performance status, heart rate, temperature, blood pressure and body weight.

(3) Adverse events have to be reported on the adverse event form, from the date of signature of informed consent until 30 days after trial treatment discontinuation. Symptoms present at baseline will be recorded on the adverse event form as well from date of informed consent (see Section 11.12).

(4) FFPE-block containing sufficient tumour-material for central confirmation of RET-rearrangement. Suitable material encompasses any biopsy material, resection material and cytoblocks.

(5) Upon progression, a re-biopsy of a progressive lesion is strongly encouraged. The biopsy material should be fresh-frozen upon extraction.

(6) Plasma samples, re-biopsy sample and whole blood will be locally stored until shipment to the central laboratory.

(7) ALT, AST, bilirubin, ALP should be measured at every treatment visit (week 0 and then every 2 weeks (±3 days) for the first 12 weeks and every 4 weeks thereafter. GGT and LDH will be repeated if clinically indicated according to local standards.

(8) Urine samples will be collected as follows: first morning urine sample for baseline and end of treatment visit, spot urine for rest of visits.

(9) CPK to be measured at treatment visit 1, 2 and 3 (week 0, 2 and 4) and then repeated if clinically indicated.

(10) Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine beta HCG pregnancy test within 7 days before enrolment into the trial and within 3 days before alectinib treatment start. Pregnancy testing has to be repeated during the duration of the trial treatment according to local standard.

Female patients of child-bearing potential, or women of child-bearing potential who are partners of male patients receiving alectinib, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of alectinib. Any pregnancy occurring during treatment or within 3 months following the last dose of alectinib must be reported including its outcome.

(11) 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.

(12) All patients must have a contrast enhanced CT thorax and upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) at baseline during screening within 6 weeks before enrolment. CT scan will be repeated 8 weeks (±4 days) after first dose of alectinib and then every 8 weeks (±4 days) until disease progression. The same imaging technique, acquisition, and processing parameters should be used in a patient throughout the trial. In the case that a CT scan had to be done earlier or later than scheduled, effort should be made to return to the original CT schedule.

(13) Treatment visits are planned at treatment start (week 0) and then every 2 weeks (±3 days) for the first 12 weeks and every 4 weeks (±3 days) thereafter. Patient diary should be checked and capsules returned should be counted.

(14) Within 30 days following the decision to stop trial treatment or within 30 days after planned treatment start if treatment never started.

(15) Follow-up visits after treatment stop. Before progression: every 8 weeks (±4 days), coinciding with imaging visits.

(16) Patients with progression that ends trial treatment will be followed up every 12 weeks (±2 weeks) starting from date of progression until trial end (e.g. until 6 months after inclusion of the last patient).

(17) Evaluations will also be repeated if clinically indicated according to local standards.

(18) CT to be repeated if not done within 6 weeks prior to end of treatment visit.

(19) In case of treatment stop for reason other than progressive disease, CT needs to be repeated every 8 weeks until progression.

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4. Background and rationale

4.1. NSCLC targeted treatment strategies

Despite advances in the treatment of non-small cell lung cancer (NSCLC) over the past several decades, only small incremental overall survival benefits have been demonstrated and treatments beyond first-line remain limited in unselected NSCLC.

In 2004 the discovery of the Epidermal Growth Factor Receptor (EGFR) mutations in NSCLC and their predictive value for therapy with EGFR tyrosine kinase inhibitors (TKIs) opened the way to an intense program of research on lung cancer, aiming at identifying other genomic or protein alterations that could be used as targets for treatment. Subsequently, genetic rearrangements of the anaplastic lymphoma kinase (ALK) gene in lung cancer and its oncogenic features were discovered in 2007. The impressive clinical results obtained with the inhibition of ALK and EGFR kinases compared to classical chemotherapy further supported the hypothesis that targeting signaling pathways aberrantly active in cancer cells, might lead to a better outcome of therapy for molecularly selected lung cancer patients. However, EGFR mutations and ALK translocations cover only 15-20% of NSCLC in Western populations, calling for discovery and development of novel targets. Studies on molecular alterations of lung tumours highlighted peculiar differences of biomarkers expression and role in the several histotypes of lung cancer. Adenocarcinoma (ADC) is the most prevalent histologic subtype among lung tumours and certainly the most characterized for its molecular features. To date, a targetable alteration may be recognized in 20-30% of adenocarcinomas in Caucasian patients.

4.2. RET fusion in NSCLC

After the discovery of ALK fusions, other genes have been found genetically rearranged in lung cancer. Gene fusions may occur as consequence of chromosomal translocation, inversion or interstitial deletion. Oncogenic rearrangements may cause the expression of new proteins or of a protein with different activity than the native one. Fusion can bring a gene under the control of a strong promoter, causing aberrant expression of a protein in cells where usually the protein has no or low expression.

The RET gene is located on chromosome 10 and encodes for a transmembrane receptor with tyrosine kinase activity. It is involved in cell proliferation, migration, differentiation, and in neuronal navigation. Germline and somatic mutations of RET are known to cause the multiple endocrine neoplasia type 2 (MEN2) syndrome and are involved in the tumourigenesis of sporadic medullary thyroid cancer. Furthermore, RET rearrangements are involved in sporadic and radiation induced papillary thyroid carcinoma. RET fusions are transforming in vitro and in vivo, and inhibition of RET in RET-rearranged lung cancer cells leads to suppressed viability.[1]

RET rearrangements have been identified in lung ADC as well, with an incidence of 1-2%.[2-4] Several genes, such as KIF5B, CCDC6, NCO4 and TRIMM33,[2,3,5] can act as fusion partners. RET-positive lung carcinomas are more common in poorly differentiated tumours and in never-smokers. Therapeutically, several multiple kinases inhibitors, such as vandetanib (Astrazeneca, England), cabozantinib (Exelis Inc. USA), ponatinib (Ariad, USA), axitinib

(Pfizer, USA), sunitinib (Pfizer, USA), sorafenib (Bayer Healthcare, Germany), and alectinib (Roche, Switzerland) are potentially able to inhibit RET kinase function. Phase III trials data in biologically unselected NSCLC are available for some of these agents both as monotherapy and in combination. However, all the results from these studies were negative and none of the drugs was approved for lung cancer treatment, probably due to the absence of genotypic selection. On the other hand, some case reports describe anecdotal responses to treatment with vandetanib and cabozantinib in RET-positive lung cancer patients.[5-11]

4.3. Alectinib

Alectinib (RO5424802, Alecensa®) is a highly selective next generation ALK inhibitor. In preclinical in vitro enzyme inhibition assays alectinib has been shown to selectively inhibit ALK, but also RET.[12] The compound also showed high antitumour activity both in vitro and in vivo against tumour cell lines with some type of ALK gene alteration, including NSCLC and anaplastic large cell lymphoma lines harbouring an ALK translocation and a neuroblastoma line harbouring amplified ALK gene.[12]

The clinical development program for alectinib, comprises several phase I-III studies in patients with ALK-positive NSCLC:[13] Two phase I/II studies (NP28761/AF-002JG and NP28673) evaluating alectinib in crizotinib-failed ALK-positive NSCLC patients are being conducted in North America, Europe, and other countries. One hundred and thirty four patients are enroled in study NP28761 (data cut-off date: 22 January 2016) and 149 patients are enroled in study NP28673 (data cut-off date: 01 February 2016), both of which are ongoing.

The first in human phase I/II study in ALK-positive crizotinib-naïve NSCLC, AF-001JP, is being conducted in Japan. The AF-001JP study is ongoing, with 70 patients enroled. Study WP29158 is a phase 1b study of the safety and pharmacology of atezolizumab administered with erlotinib or alectinib in patients with advanced NSCLC.[15]

Clinical pharmacology studies have also been conducted in healthy subjects and patients. A study (NP29783) to evaluate the pharmacokinetics of alectinib in subjects with moderate to severe hepatic impairment is currently ongoing.

The global phase III study (BO28984) to evaluate alectinib versus crizotinib in patients with treatment-naïve advanced ALK-positive NSCLC is ongoing. A separate phase III study (JO28928) with a design similar to the BO28984 study in patients with ALK-positive NSCLC who are treatment-naïve or have received one line of standard chemotherapy is ongoing in Japan.

A phase III study (MO29750) was started in October 2015 to evaluate alectinib versus pemetrexed or docetaxel in patients with ALK-positive advanced NSCLC, previously treated with platinum-based chemotherapy and crizotinib.

A phase III study (YO29449) was started in June 2016 to evaluate the efficacy and safety of alectinib versus crizotinib and to evaluate the pharmacokinetics of alectinib in Asian participants with treatment-naive ALK-positive advanced NSCLC.

In addition, there is an ongoing post marketing drug use surveillance (ALC1401) study in Japan.

4.3.1. Alectinib for RET-rearranged NSCLC

Preclinical studies have recently shown that alectinib has potent anti-tumour activity in RET-rearranged NSCLC. In a kinase inhibitory assay, alectinib inhibited RET kinase activity with an IC50 of 4.8 nM, and in an ATP-competitive binding assay, alectinib bound to RET at a dissociation constant value of 7.6 nM. The IC50 for alectinib for RET kinase appears to be higher than for ALK kinase (1.9 nM), which may indicate a need for a higher dose of alectinib than currently approved for ALK+ NSCLC (600 mg orally twice a day) to ensure efficacious/therapeutic concentrations are achieved in this population.[12]

To date, a unique small clinical report of alectinib activity in RET-rearranged NSCLC is available. Recently, in the Journal of Thoracic Oncology', the Massachusetts General Lung Group reported on four RET-rearranged advanced NSCLC patients who were treated with alectinib (600 mg twice daily, N=3; 900 mg twice daily, N=1) as part of single-patient, compassionate use protocols or off-label use of the commercially available drug. Three of the four had received prior RET TKIs including cabozantinib and experimental RET inhibitors. In total, they describe two (50%) objective radiographic responses following treatment with alectinib (one confirmed and one unconfirmed), with durations of therapy of 6 months and 5+ months (treatment ongoing), respectively. Notably, one of these two patients was dose-escalated to alectinib 900 mg twice daily and had clinical improvement in central nervous system metastases. In addition, one patient (25%) experienced a best response of stable disease lasting ~6 weeks (drug discontinued for toxicity). A fourth patient who was RET-TKI-naïve had primary progression on alectinib. Therefore, alectinib demonstrated preliminary antitumour activity in advanced RET-rearranged NSCLC patients.[10]

4.4. Overall risk / benefit assessment

Distinct subtypes of NSCLC are driven by a specific genetic alteration and are known to be sensitive to inhibition of the corresponding activated oncogenic pathway. RET rearrangements have been identified in lung ADC with an incidence of 1-2% and several multiple kinases inhibitors are potentially able to inhibit RET kinase function.

Alectinib has been administered in several clinical trials and it has been shown that it was generally well tolerated and had an acceptable safety profile. Section 10 of this protocol summarizes potential risks based upon non-clinical toxicity and clinical patient studies with alectinib with further detailed information available in the IB for alectinib.

4.5. Rationale for trial design and alectinib dose

4.5.1. Rationale for patient selection

To ensure an appropriate and standardised patient population, all patients must have histologically or cytologically documented advanced NSCLC (recurrent stage IV) with locally tested RET rearrangement after at least one previous line of platinum-based systemic therapy. RET rearrangement will later be centrally confirmed.

4.5.2. Rationale for alectinib dose

Based on the total, current, safety, pharmacokinetic and preliminary efficacy data, 600 mg alectinib twice daily was selected as the recommended dose. Please refer to the latest version of the ***Alectinib IB*** for additional details.

Dose finding studies

In study NP28761/AF-002JG, no dose-limiting toxicities (DLTs) were observed in the dose-escalation cohorts, up to a dose of 900 mg twice daily. However, 2 patients in the subsequent 900 mg twice daily bridging cohort experienced a DLT, one a Grade 3 headache and the other a Grade 3 neutrophil count decreased, and both patients continued study treatment at reduced dose of 600 mg twice daily. On the basis of efficacy, safety, and PK data, the recommended phase II Dose is 600 mg twice daily. No DLT for this dose was observed in the AF-001JP study.

Further dose-finding for alectinib in RET-rearranged NSCLC is currently conducted in two separate studies:

A phase I/II study of alectinib in RET-rearranged NSCLC or RET-mutated thyroid cancer (NCT03131206) and a multicenter phase II/III study (NCT03178552) evaluating the efficacy and safety of multiple targeted therapies as treatments for patients with advanced or metastatic NSCLC harboring actionable somatic mutations detected in blood (B-FAST: Blood-First Assay Screening Trial). The B-FAST trial includes a dose finding phase for alectinib. Participants in the RET+ NSCLC cohort receive a starting dose of 900 mg orally BID of alectinib, with one additional dose-escalation group to 1200 mg orally if the recommended phase II dose is not established in any other clinical study.

As soon as the 900 mg alectinib twice daily has proven to be safe in any of these dose finding studies, the ETOP 12-17 ALERT-lung protocol will be amended to this higher dose.

5. Objectives and endpoints

5.1. Primary objective

The primary objective is to assess the efficacy of alectinib in terms of best overall response (OR) assessed by RECIST 1.1., from the start of trial treatment across all time points until the end of trial treatment.

5.2. Secondary objectives

5.2.1. To evaluate secondary measures of clinical efficacy including disease control, progression-free survival (PFS), and overall survival (OS).

5.2.2. To assess the safety and tolerability of the treatment.

5.3. Primary endpoint

5.3.1. Best overall response (OR = CR or PR), per investigator assessment, according to RECIST 1.1.

5.4. Secondary endpoints

5.4.1. Best overall response per independent review.

5.4.2. Disease control at 24-weeks: best overall response of CR or PR, or SD (or non-CR/non-PD in the case of non-measurable disease only)

5.4.3. PFS defined as the time from the date of enrolment until documented progression or death, if progression is not documented

5.4.4. OS defined as time from the date of enrolment until death from any cause

5.4.5. Safety and tolerability (see Section 13.5)

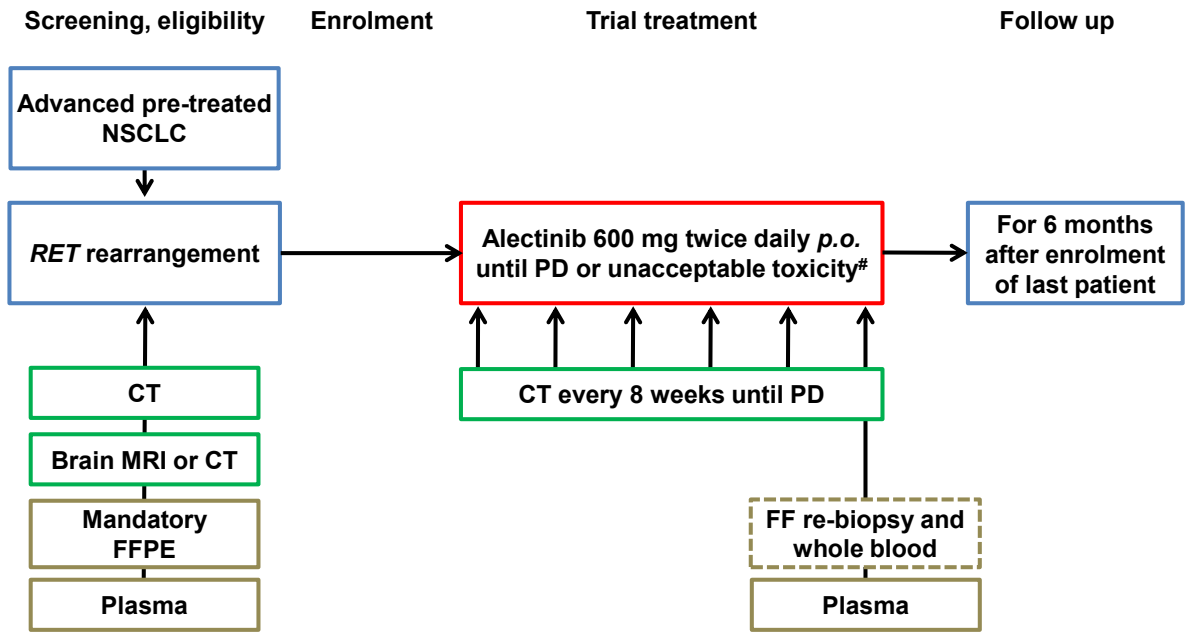
5.5. Correlative studies

Further exploratory analyses include description of primary and secondary outcomes for patient subgroups of interest, as defined by patient or tumour characteristics or different levels of biomarkers examined.

6. Trial design, duration and termination

6.1. Trial design

ALERT-lung is a single arm, multicentre phase II trial evaluating the activity of alectinib as second-line treatment of pretreated RET-rearranged advanced NSCLC.



treatment may continue beyond progression if there is clinical benefit

6.2. Sample size and trial duration

A total of 44 enroled patients are required and based on the low incidence of RET rearrangement in NSCLC (1-2%) approximately 4500 patients are expected to be screened in order to find enough eligible patients.

The patients will be recruited from approximately 30 centres in eight different countries in Europe.

Clinical visits are expected to span approximately 44 months after enrolment of the first patient. Assuming an accrual rate of approximately 1 patient per month and a start-up period of 6 months as the trial is activated by participating centres, the final trial report is expected to be available approximately 5 years after the enrolment of the first patient.

7. Patient selection

Written informed consent (IC) must be signed and dated by the patient and the investigator prior to any trial-related intervention and biomaterial submission for central review to confirm RET-rearrangement.

7.1. Inclusion criteria

7.1.1. Histologically or cytologically documented non-small cell lung carcinoma

7.1.2. Advanced disease defined as recurrent stage IV (according to 8th TNM classification) or recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemo-radiation therapy for locally advanced disease)

7.1.3. At least one prior platinum-based systemic regimen: Adjuvant or neoadjuvant or definitive platinum-based chemo-radiotherapy treatments are considered as a line of treatment only if completed less than 6 months before enrolment. Maintenance therapy following platinum doublet-based chemotherapy is not considered a separate regimen of therapy.

7.1.4. RET rearrangement detected by FISH, Nanostring or by parallel-sequencing on FFPE tumour tissue assessed locally.

7.1.5. Availability of FFPE tumour material for central confirmation of RET-rearrangement

7.1.6. Measurable or non-measurable, but radiologically evaluable (except for skin lesions) disease according to RECIST v1.1 criteria

7.1.7. Age ≥18 years

7.1.8. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2

7.1.9. Life expectancy >3 months

7.1.10. Adequate haematological function:

- Haemoglobin ≥9 g/dL
- Neutrophil count ≥1.5 $\times 10^9$/L
- Platelet count ≥100 $\times 10^9$/L
- WBC ≥2 $\times 10^9$/L

7.1.11. Adequate renal function: Calculated creatinine clearance ≥45 mL/min (according to Cockcroft-Gault formula below).

Cockcroft-Gault formula

$$\frac{\text{mL}}{\text{min}} = \frac{(140\text{-age[years]}) \times \text{actual body weight [kg]}}{72 \times \text{Creatinine}_{\text{serum}} \left(\frac{\text{mg}}{\text{dL}}\right)} (\times 0.85 \text{ if female})$$

7.1.12. Adequate liver function:

- Total bilirubin ≤2× ULN (except patients with Gilbert Syndrome, who can have total bilirubin ≤3.0 mg/dL)
- ALT and AST ≤3× ULN (≤5× ULN for patients with concurrent liver metastasis)

7.1.13. Patient capable of proper therapeutic compliance, and accessible to correct follow-up.

7.1.14. Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine beta HCG pregnancy test within 7 days before enrolment into the trial and within 3 days before alectinib treatment start.

7.1.15. Sexually active men and women of childbearing potential must use an effective contraceptive method (intrauterine devices without hormones, bilateral tubal occlusion, vasectomized partner or total abstinence) during the trial treatment and for a period of at least 3 months following the last dose of alectinib (see Section 10.6.1. for effective contraceptive methods).

7.1.16. Recovered from any previous therapy related toxicity to Grade ≤1 at date of enrolment (except for recovery to Grade ≤2 of alopecia, fatigue, creatinine increased, lack of appetite or peripheral neuropathy)

7.1.17. Written Informed Consent (IC) for trial treatment must be signed and dated by the patient and the investigator prior to any trial-related intervention.

7.2. Exclusion criteria

7.2.1. Untreated, active CNS metastases

7.2.2. Carcinomatous meningitis

7.2.3. Any previous (in the past 3 years) or concomitant malignancy EXCEPT adequately treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or bladder, in situ ductal carcinoma of the breast

7.2.4. Any serious diseases or clinical conditions, including but not limited to uncontrolled active infection and any other serious underlying medical processes, that could affect the patient's capacity to participate in the trial

7.2.5. Liver disease characterized by:

- ALT or AST >3 × ULN (>5 × ULN for patients with concurrent liver metastasis) confirmed on two consecutive measurements or
- Impaired excretory function (e.g., hyperbilirubinaemia) or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminaemia, ascites, and bleeding from oesophageal varices or
- Acute viral or active autoimmune, alcoholic, or other types of acute hepatitis

7.2.6. Patients with baseline symptomatic bradycardia

7.2.7. Previous treatment with any RET TKI or RET targeted therapy

7.2.8. Known EGFR, ALK, ROS, and BRAF mutation (in addition to RET rearrangement)

7.2.9. Any concurrent systemic anticancer therapy

7.2.10. Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post major bowel resection

7.2.11. History of hypersensitivity to any of the additives in the alectinib drug formulation

7.2.12. Known HIV positivity or AIDS-related illness

7.2.13. Women who are pregnant or in the period of lactation.

8. Investigational medicinal products

Alectinib is the investigational medicinal products (IMPs) in this trial.

Complete details of the IMP logistics, distribution, packaging, labelling and handling as well as accountability are described in the ***ALERT-lung Drug Supply Manual***.

8.1. Alectinib

Alectinib (also RO5424802 or CH5424802) is a small molecule, highly selective, and potent oral next generation ALK inhibitor with a benzo[b]carbazole scaffold. In enzyme inhibition assays performed in vitro, this compound has been shown to selectively inhibit ALK, but also RET.

8.2. Formulation

Please refer to the current version of the ***Alectinib IB*** for pharmaceutical formulation information.

Clinical supplies will be provided by Roche. For details please refer to the ***ALERT-lung Drug Supply Manual***.

8.3. Packaging and labelling

Clinical supplies will be affixed with a clinical trial label in accordance with regulatory requirements.

8.4. Storage and handling

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Clinical supplies must be stored in the original container in order to protect from moisture. The Principal Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any

applicable laws and regulations. See the ***ALERT-lung Drug Supply Manual*** for complete details.

9. Trial treatments

9.1. Alectinib administration

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.

9.1.1. Missed dose of alectinib

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. If vomiting occurs after taking a dose of alectinib, patients should take the next dose at the scheduled time. Alectinib treatment should be permanently discontinued if the treatment interruption exceeds 21 consecutive days.

Guidelines for dose modifications and treatment interruptions or discontinuation due to specified adverse events are provided in Section 10.3.

9.2. Patient compliance

9.2.1. Treatment compliance

Alectinib will be given in accordance with the protocol and the instructions of a site investigator or pharmacist.

The appropriate number of alectinib capsules will be provided to patients to be self-administered at home. Patients should be instructed to use the patient diary to record every self-administration as well as any symptoms and to bring the patient diary to every visit at the clinic.

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.

The investigator and/or ETOP can withdraw a patient from the trial in the event of serious and persistent non-compliance, which jeopardizes the patient's safety or renders trial results for this patient unacceptable.

Patients who do not take a minimum 50% of the daily dose of alectinib, unless due to exceptional circumstances, should be discussed with ETOP and be evaluated for compliance.

9.2.2. Visit compliance

Patients who do not attend a minimum of 75% of scheduled trial visits, unless due to exceptional circumstances, should be discussed with ETOP and evaluated for compliance.

9.3. Treatment duration

Patients remain on treatment until one of the following events, whichever occurs first:

- Documented progression according to RECIST v1.1 (except if the patient may still derive clinical benefit as per investigator's decision).
- Unacceptable toxicity to alectinib
- Medical condition that prevents further treatment
- Patient withdraws consent
- Patient becomes pregnant
- Trial termination (approximately 6 months after inclusion of the last patient)

10. Safety of alectinib

Alectinib has minor influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience symptomatic bradycardia (e.g., syncope, dizziness, and hypotension) or vision disorders while taking alectinib.

10.1. Summary of the safety profile

The safety of alectinib has been evaluated in 253 patients in pivotal phase II clinical trials (NP28761, NP28673) with ALK-positive non-small cell lung cancer (NSCLC) treated with the recommended dose of 600 mg twice daily. The median duration of exposure to alectinib was 11 months.

The most common adverse drug reactions (ADRs) (≥20%) were constipation (36%), oedema (34%, including oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema), myalgia (31%, including myalgia and musculoskeletal pain) and nausea (22%).

A detailed safety profile of alectinib is provided in the most recent version of the alectinib Investigator's Brochure.

10.2. Description of selected adverse events

Events described below will be closely monitored and represent selected AEs for this trial.

10.2.1. Abnormal renal function and acute kidney injury

In the 2-week non-human primate study at 60 mg/kg alectinib, an increase in creatinine was observed but no changes were observed in histopathology. In all other non-human primate studies, no changes in creatinine were observed. Serum creatinine increases and/or decreases in GFR have been reported for other ALK inhibitors (crizotinib, ceritinib). In the pooled analysis of the pivotal studies NP28761 and NP28673, serum creatinine increases have been reported in 17/253 patients (6.7%) treated with 600 mg alectinib twice daily. All but one event were of Grade 1 or 2 severity. A low rate of dose modification (including dose reduction, treatment interruption and withdrawal) due to these events was observed in approximately 2% of the patients. No cases of renal failure have been reported in the patients treated with 600 mg alectinib twice daily. In the evaluation of the safety laboratory tests, blood creatinine

displayed an increase in median values which remained within the normal range. In study AF-001JP, a total of 19/58 patients (32.8%) treated with 300 mg alectinib twice daily reported blood creatinine increased, all of Grade 1 or 2 severity. Blood creatinine tended to increase slightly after treatment start but then generally remained at around 1.5-fold the site upper limit of baseline. For 3/58 patients (5.2%), renal impairment (not serious, Grade 1) was reported. See Section 10.3 for the management of abnormal renal function.

10.2.2. Anaemia

Haematologic findings were observed in both the rat and monkey 4-week and 13-week toxicity studies and findings in the 13-week studies were similar to those of the 4-week studies. Findings were at or close to clinically relevant exposures. Findings in the 13-week rat study included abnormal RBC morphology, large platelets in blood, macrophage/erythrophagy/blood absorption in lymph nodes, decreased lymphocyte in lymphoid tissues, and prolongation of prothrombin time. Findings in the 13-week monkey study included decreased RBCs with or without decreased haemoglobin concentration and haematocrit. In the 13-week toxicity study in rats, but not in monkeys, ileal haemorrhage accompanied by prolongation of the clotting time was noted. Haematologic adverse effects such as anaemia, thrombocytopenia, leukopenia and neutropenia have been observed with ALK inhibitors, including crizotinib and ceritinib. In the pooled analysis of the pivotal studies NP28761 and NP28673, anaemia was observed for 40/253 (15.8%; 1 serious) of the patients treated with 600 mg alectinib BID. The majority of events were Grade 1 or 2; four patients (1.6%) experienced a Grade 3 event, which did not require changes to study drug dosing, and one patient (0.4%) experienced a serious Grade 4 event, which was assessed by the Investigator to be unrelated to alectinib. A generally mild decrease of median haemoglobin levels was observed during the first month of treatment with alectinib, with median levels stabilizing at a level slightly below the normal range.

In Study AF-001JP, 3/58 (5.2%) patients treated with 300 mg alectinib BID experienced anaemia (with 1 case [1.7%] reported as Grade 3) and 2/58 (3.4%) patients had haemoglobin decreased. Haematologic parameters including RBC, neutrophil, lymphocyte, and platelet counts will be monitored routinely in clinical trials. Study-specific inclusion, exclusion and withdrawal criteria are included in study protocols.

10.2.3. Bradycardia

Cases of bradycardia (7.9%) of Grade 1 or 2 have been reported in patients treated with alectinib in pivotal phase II clinical trials (NP28761, NP28673). There were 44 of 221 patients (20%) treated with alectinib who had post-dose heart rate values below 50 beats per minute. Patients who develop symptomatic bradycardia should be managed as recommended in Section 10.3. No case of bradycardia led to withdrawal from alectinib treatment.

10.2.4. Gastrointestinal effects

Constipation (36%), nausea (22%), diarrhoea (18%) and vomiting (13%) were the most commonly reported gastrointestinal (GI) reactions. Most of these events were of mild or moderate severity; Grade 3 events were reported for diarrhoea (1.2%), nausea (0.4%), and vomiting (0.4%). These events did not lead to withdrawal from alectinib treatment. Median time to onset for constipation, nausea, diarrhoea, and/or vomiting events was 18 days. The

events declined in frequency after the first month of treatment. See Section 10.3 for management of gastrointestinal events.

10.2.5. Hepatotoxicity

The finding of an elevated ALT or AST (≥3× baseline value) in combination with either an elevated total bilirubin (≥2× ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law), see Section 11.7.1.

Patients should be monitored for liver function and investigators must report as an adverse event of special interest (AESI) the occurrence of either of the following:

- Treatment-emergent ALT or AST (≥3× baseline value in combination with total bilirubin ≥2× ULN (of which ≥35% is direct bilirubin)
- Treatment-emergent ALT or AST ≥3× baseline value in combination with clinical jaundice

See also Section 10.3 for the management of hepatotoxicity events.

In the pivotal phase II clinical trials (NP28761, NP28673) two patients with Grade 3-4 AST/ALT elevations had documented drug induced liver injury by liver biopsy. One of these cases led to withdrawal from alectinib treatment. Adverse reactions of increased AST and ALT levels (16% and 14% respectively) were reported in patients treated with alectinib in pivotal phase II clinical trials (NP28761, NP28673). The majority of these events were of Grade 1 and 2 intensity, and events of Grade ≥3 were reported in 2.8% and 3.2% of the patients, respectively. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of alectinib treatment (reported for 1.2% and 3.2% of the patients, respectively) or dose reduction (1.6% and 0.8%, respectively). In 1.2% and 1.6% of the patients, AST and ALT elevations, respectively, led to withdrawal from alectinib treatment.

Adverse reactions of bilirubin elevations were reported in 17% of the patients treated with alectinib in pivotal phase II clinical trials (NP28761, NP28673). The majority of the events were of Grade 1 and 2 intensity; Grade 3 events were reported in 3.2% of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of alectinib treatment (4.7% of the patients) or dose reduction (2.8%). In 4 patients (1.6%), bilirubin elevations led to withdrawal from alectinib treatment.

Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred in one patient (0.2%) treated in alectinib clinical trials.

10.2.6. Interstitial lung disease (ILD) / pneumonitis

Severe ILD/pneumonitis occurred in patients treated with alectinib. In the pivotal phase II clinical trials (NP28761, NP28673), 1 out of 253 patients treated with alectinib (0.4%) had a Grade 3 ILD. This event led to withdrawal from alectinib treatment. There were no fatal cases of ILD. Patients should be monitored for pulmonary symptoms indicative of pneumonitis. See Section 10.3 for the management of ILD events.

10.2.7. Oedema

Most tyrosine kinase inhibitors have been associated with oedema, including ALK inhibitors, such as crizotinib and ceritinib. In the pooled analysis of the pivotal studies NP28761 and NP28673, oedema was observed in 85/253 (33.6%; 2/253 Grade ≥3) patients treated with 600 mg alectinib twice daily. None of the events were reported as serious, and none required withdrawal from or interruption of treatment. Three patients (1.2%) required a dose reduction due to oedema. In study AF-001JP, 6 events of oedema were reported in 58 patients who received treatment with 300 mg twice daily. See Section 10.3 for the management oedema events.

10.2.8. Photosensitivity

Results of an in vitro phototoxicity study indicated that alectinib may have a phototoxic potential. Photosensitivity has been reported also with ALK-inhibitor (ceritinib). In the pooled analysis of the pivotal studies NP28761 and NP28673, photosensitivity reactions (photosensitivity and sunburn) were observed for 30/253 (11.9%) patients treated with 600 mg alectinib twice daily. All of these events were Grade 1 or 2 and none were serious. Frequency of dose interruptions (0.4%) due to these events was low; there were no such events leading to withdrawal from treatment. No cases of photosensitivity were reported in study AF-001JP. See Section 10.3 for the management of photosensitivity.

10.2.9. Rash

Skin rash has been reported with ALK inhibitors (ceritinib and crizotinib). In the pooled analysis of the pivotal studies NP28761 and NP28673, rash (generalized rash, rash maculopapular, dermatitis acneiform, erythema, rash papular, rash pruritic, and rash macular) was observed for 51/253 (20.2%) patients treated with 600 mg alectinib twice daily. All except 1 of these events were Grade 1 or 2 and none were serious. Frequency of dose reductions (0.8%) and interruptions (1.2%) due to these events was low; there were no such events leading to withdrawal from treatment. In study AF-001JP, rash, dermatitis acneiform and maculo-papular rash were reported in 22/58 (37.9%), 1/58 (1.7%) and 3/58 (5.2%) patients treated with 300 mg twice daily, respectively, mostly of Grade 1 or 2. One case of skin exfoliation (Grade 2) and two cases of palmarplantar erythrodysaesthesia syndrome (one Grade 1 and one Grade 2) were reported. No case required any dose modification. See Section 10.3 for the management of skin disorders.

10.2.10. Severe myalgia and CPK elevations

Cases of myalgia (31%) including myalgia events (25%) and musculoskeletal pain (7.5%) have been reported in patients treated with alectinib in pivotal phase II clinical trials (NP28761, NP28673). The majority of events were Grades 1 or 2 and three patients (1.2%) had a Grade 3 event. Dose modifications of alectinib treatment due to these adverse events were only required for two patients (0.8%); alectinib treatment was not withdrawn due to these events of myalgia. Elevations of CPK occurred in 46% of 219 patients with CPK laboratory data available in pivotal phase II clinical trials (NP28761, NP28673) with alectinib. The incidence of Grade 3 elevations of CPK was 5.0%. Median time to Grade 3 CPK elevation was 14 days. Dose modifications for elevation of CPK occurred in 4.0% of patients; withdrawal from alectinib treatment did not occur due to CPK elevations. See Section 10.3 for the management of myalgia and CPK elevation.

10.2.11. Vision disorders

In the rat QWBA study, tissue radioactivity disappeared over time, following a time course comparable to that of plasma radioactivity, except for melanin-containing tissues such as uveal tract of eyes which had much higher and more sustained exposure in pigmented rats. This is consistent with what is commonly observed for lipophilic basic drugs. Vision disorders, including diplopia, photopsia, vision blurred, visual impairment, and vitreous floaters have been reported with several ALK inhibitors (ceritinib, crizotinib).

In the pooled analysis of the pivotal studies NP28761 and NP28673, vision disorders were observed for 29/253 patients (11.5%) treated with 600 mg alectinib twice daily. These included blurred vision (4.0%), visual impairment and vitreous floaters (each 2.4%), reduced visual acuity (1.6%), diplopia (1.2%) and asthenopia (0.8%). All of these events were Grade 1 or 2 and none were serious. In study AF-001JP, 17 out of the 58 patients (29.3%) treated with 300 mg twice daily had vision disorder events, including dry eye (6/58 [10.3%]), conjunctivitis (5/58 [8.6%]), increased lacrimation, blepharitis and cataract (2/58 [3.4%] each) as well as single cases of conjunctivitis allergic, vision blurred, visual impairment, maculopathy, foreign body sensation in eyes, and vitreous haemorrhage. The majority were Grade 1 or 2, except for a case of maculopathy of Grade 3, reported as an SAE, and requiring dose modification of alectinib therapy. Investigators should consider referring the patients for ophthalmological evaluation according to local clinical practice guidelines, if vision disorders persist or worsen in severity. See Section 10.3 for the management of vision disorders.

10.3. Management of alectinib related toxicities

Management of adverse events may require dose reduction, temporary interruption, or discontinuation of treatment with alectinib. The dose of alectinib should be reduced in steps of 150 mg twice daily based on tolerability. Alectinib treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose.

Dose modification advice is provided in Table 1 and Table 2 below.

Table 1 Dose reduction schedule

Reduction schedule	Dose level	Total daily dose
Starting dose	600 mg twice daily	1200 mg
First dose reduction	450 mg twice daily	900 mg
Second dose reduction	300 mg twice daily	600 mg

Table 2 Dose modification advice for specified adverse events

Event	Action to be taken
Abnormal kidney function AEs	Kidney function laboratory abnormalities are to be reported as AEs: • If, at any time during the trial treatment, eGFR decreases by >50% of the baseline visit value, the patient has to be carefully monitored. All of the underlying factors that may have

	acutely impacted serum creatinine levels need to be evaluated and corrected (e.g., dehydration, recent exposure to contrast media, increased amount of cooked meat in diet, concomitant medications affecting renal function as appropriate, etc.). • Any eGFR decrease by >50% of the baseline visit value requires repeat testing. – If, at the repeat test, the eGFR decrease is still >50% of the baseline visit value, the treatment with alectinib should be interrupted. • Alectinib treatment may be resumed with caution if the eGFR value has increased to approximately the baseline visit value.
GI tract AEs (e.g., nausea, vomiting, diarrhoea)	**Diarrhoea, nausea, and vomiting should be handled with best supportive care first before considering dose modification.** GI events are expected to be minimized by taking the study drug with a meal. In case GI events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. If GI toxicities are observed and not tolerable, treatment with study drug should be temporarily interrupted until recovery to Grade 1 or lower.
Hepatotoxicity	Liver test laboratory abnormalities are to be reported as AEs: • If ALT or AST >3× baseline, repeat testing of ALT, AST, ALP, and total bilirubin within 48 –72 hours, with inquiry about symptoms. If upon repeat testing the transaminases remain >3× baseline, but are not >5× baseline, or not accompanied with bilirubin increases, or do not match any other rule for permanent discontinuation, then monitoring can continue as per investigator judgment, and dose modification is not necessary. • At any time during the trial treatment, if symptoms compatible with liver injury are observed, liver enzymes should be measured as soon as possible.

	• Study drug treatment has to be permanently discontinued if any of the following occurs: – First observation of ALT or AST >8× ULN – ALT or AST >5× ULN for more than 2 weeks – First observation of ALT or AST >3× ULN and total bilirubin >2× ULN[#] – First observation of ALT or AST >3× ULN and the appearance of jaundice or signs of hepatic dysfunction or other symptoms (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia [>5%])[#] • Following IMP discontinuation, weekly monitoring of laboratory values should continue until the abnormal values have normalized to pre-treatment levels and/or an adequate explanation of the abnormal value is found. • Resumption of study drug is not allowed in patients discontinuing because of any of the above criteria.
Interstitial lung disease	• Patients should be monitored for pulmonary symptoms indicative of pneumonitis. • Study drug should be permanently discontinued in patients diagnosed with interstitial lung disease.
Oedema	Physical examinations will be performed routinely in clinical trials. In case oedema events occur, appropriate measures should be taken in accordance with local clinical practice guidelines.
Skin disorder AEs (e.g., phototoxicity, rash)	Patients should be advised to avoid prolonged sun exposure while taking alectinib and for at least 7 days after study drug discontinuation. Patients should also be advised to use a broad-spectrum sunscreen and lip balm of at least SPF 50 to help protect against potential sunburn.

Severe myalgia and CPK elevations	CPK laboratory abnormalities are to be reported as AEs: • Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms. • At the first occurrence of any of asymptomatic CPK values (>10× ULN, symptomatic CPK >5× ULN, or in the presence of severe muscular symptoms with CPK >ULN but ≤5× ULN) at any time during the trial treatment, the patient requires monitoring of the CPK values until they are normalized to pre-treatment levels or a reasonable explanation for the CPK elevation and the symptoms is established.
Vision disorders	Investigators should consider referring patients for an ophthalmological evaluation according to local clinical practice guidelines if vision disorders persist or worsen in severity and should advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder.
Other AEs (including bradycardia and anaemia) or laboratory abnormalities:	**Grade 3 or 4:** • Temporarily interrupt alectinib for a maximum of 3 weeks. • If improvement to Grade ≤1 or baseline does not occur within 21 days, permanently discontinue alectinib. • First episode: If improvement to Grade ≤1 or baseline does not occur within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule) twice daily (to a total dose of 450 mg twice daily). • Second episode: If improvement to Grade ≤1 or baseline does not occur within 21 days, decrease the current dose of alectinib by another 150 mg (1

	capsule) twice daily (to a total dose of 300 mg twice daily). • Third episode: Permanently discontinue alectinib. **Grade 2** (except any symptoms and signs that can be corrected with supportive care): • Temporarily interrupt alectinib and resume if recovering to Grade ≤1 or baseline if. • First episode: If improvement to Grade ≤1 or baseline occurs within 10 days, continue same dose of alectinib. If improvement occurs after 10 days, decrease the current dose of alectinib by 150 mg (1 capsule) twice daily when resuming treatment (to a total dose of 450 mg twice daily). • Second episode: If improvement to Grade ≤1 or baseline does not occur within 10 days, decrease the current dose of alectinib by 150 mg (1 capsule) twice daily (to a final dose of 450 mg twice daily, or 300 mg twice daily if dose was reduced to 450 mg twice daily after first episode). If improvement occurs after 10 days, decrease the current dose of alectinib by 300 mg (2 capsules) when resuming treatment (to a total dose of 300 mg twice daily, or 150 mg twice daily if dose was reduced to 450 mg twice daily after first episode). • Third episode: Permanently discontinue alectinib. **Grade 1:** no action required

AE: adverse event; twice daily: twice a day; ANC: absolute neutrophil count; eGFR: estimated glomerular filtration rate; GI: gastrointestinal.

Note: Pre-existing pleural effusion will not be considered as an adverse event.

Note: # refer to Section 11.7 Adverse Events of Special Interest

10.4. Contraindications

Hypersensitivity to alectinib or to any of the excipients (see the ***Alectinib IB*** for details).

10.5. Effects of other medicinal products on alectinib

Based on in vitro data, CYP3A4 is the primary enzyme mediating the metabolism of both alectinib and its major active metabolite M4, and CYP3A contributes to 40% − 50% of total hepatic metabolism. M4 has shown similar in vitro potency and activity against ALK.

10.5.1. CYP3A inducers

Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong CYP3A inducer, with a single oral dose of 600 mg alectinib reduced alectinib Cmax, and AUCinf by 51% and 73% respectively and increased M4 Cmax and AUCinf 2.20 and 1.79-fold respectively. The effect on the combined exposure of alectinib and M4 was minor, reducing Cmax and AUCinf by 4% and 18%, respectively. Based on the effects on the combined exposure of alectinib and M4, no dose adjustments are required when alectinib is co-administered with CYP3A inducers. Appropriate monitoring is recommended for patients taking concomitant strong CYP3A inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort [Hypericum perforatum]).

10.5.2. CYP3A inhibitors

Co-administration of multiple oral doses of 400 mg posaconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 300 mg alectinib increased alectinib exposure Cmax and AUCinf by 1.18 and 1.75-fold respectively, and reduced M4 Cmax and AUCinf by 71% and 25% respectively .The effect on the combined exposure of alectinib and M4 was minor, reducing Cmax by 7% and increasing AUCinf 1.36-fold. Based on the effects on the combined exposure of alectinib and M4, no dose adjustments are required when alectinib is co-administered with CYP3A inhibitors. Appropriate monitoring is recommended for patients taking concomitant strong CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole nefazodone, grapefruit or Seville oranges).

10.5.3. Medicinal products that increase gastric pH

Multiple doses of esomeprazole, a proton pump inhibitor, 40 mg once daily, demonstrated no clinically relevant effect on the combined exposure of alectinib and M4. Therefore, no dose adjustments are required when alectinib is co-administered with proton pump inhibitors or other medicinal products which raise gastric pH (e.g. H2 receptor antagonists or antacids).

10.5.4. P-gp substrates

In vitro, alectinib and its major active metabolite M4 are inhibitors of the efflux transporter P-glycoprotein (P-gp). Therefore, alectinib and M4 may have the potential to increase plasma concentrations of co-administered substrates of P-gp. When alectinib is co-administered with P-gp substrates (e.g., digoxin, dabigatran etexilate, topotecan, sirolimus, everolimus, nilotinib and lapatinib), appropriate monitoring is recommended.

10.5.5. BCRP substrates

In vitro, alectinib and M4 are inhibitors of the efflux transporter Breast Cancer Resistance Protein (BCRP). Therefore, alectinib and M4 may have the potential to increase plasma concentrations of co-administered substrates of BCRP. When alectinib is co-administered

with BCRP substrates (e.g., methotrexate, mitoxantrone, topotecan and lapatinib), appropriate monitoring is recommended.

10.5.6. CYP substrates

In vitro, alectinib and M4 show weak time-dependent inhibition of CYP3A4, and alectinib exhibits a weak induction potential of CYP3A4 and CYP2B6 at clinical concentrations.

Multiple doses of 600 mg alectinib had no influence on the exposure of midazolam (2 mg), a sensitive CYP3A substrate. Therefore, no dose adjustment is required for co-administered CYP3A substrates.

A risk for induction of CYP2B6 and PXR regulated enzymes apart from CYP3A4 cannot be completely excluded. The effectiveness of concomitant administration of oral contraceptives may be reduced.

10.6. Contraception, nursing, pregnancy

10.6.1. Contraception

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.

Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Examples of effective contraceptive methods with a failure rate of <1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.

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 must be reported following procedures detailed in Section 11.13. Also any pregnancy that occurs in a female partner of a male trial participant must be reported.

Patients should be informed that taking the trial medication may involve unknown risks to the foetus if pregnancy were to occur during the trial. In order to participate in the trial they must adhere to the contraception requirement (described above) for the duration of the trial up to at least 3 months after the last dose of any alectinib. If there is any doubt whether a patient will reliably comply with the requirements for contraception, that patient should not be entered into the trial.

10.6.2. Use in pregnancy

If a patient inadvertently becomes pregnant while on trial treatment, trial treatment will be stopped immediately for the patient and the event must be reported immediately, see

Section 11.13. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to ETOP without delay and within 24 hours if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or newborn to ETOP.

10.6.3. Use in nursing women

It is unknown whether alectinib and its metabolites are excreted in human milk. A risk to the newborn/infant cannot be excluded. Patients who are breast-feeding are not eligible for the trial.

11. Adverse event and serious adverse event reporting

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

The main criterion for tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the CTCAE version 4.0.

The CTCAE is available for downloading on the internet at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

Detailed reporting instructions are indicated in Section 11.12.

11.1. Adverse event (AE)

An adverse event (AE) is defined as any untoward medical occurrence that occurs from the date of signature of informed consent until 30 days after all trial treatment discontinuation, regardless of whether it is considered related to a medication.

An AE can therefore be any of the following:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether considered related to the IMP or not.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in trial treatment or concomitant treatment or discontinuation from IMP.

- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of trial treatment (e.g., screening invasive procedures such as biopsies)

Any grade of any observed AE should be reported on the ***AE eCRFs***. Please see Section 11.12 for details.

11.2. Adverse reaction (AR)

An adverse reaction (AR) is defined as "any noxious and unintended response to an IMP related to any dose administered".

All adverse events judged by either the reporting investigator or the sponsor (ETOP) as having a reasonable causal relationship (see Section 11.9) to an IMP qualify as adverse reactions. The expression suspected/related means to convey in general that there is evidence or argument to suggest a causal relationship to the trial treatment.

11.3. Unexpected adverse reaction (UAR)

An unexpected adverse reaction (UAR) is any adverse reaction, the nature, or severity of which is not consistent with the applicable product information.

When the outcome of the adverse reaction is not consistent with the ***Alectinib IB*** or summary of product characteristics (SmPC) this adverse reaction should be considered as unexpected.

11.4. Serious adverse events (SAE)

A serious adverse event (SAE) is defined as any undesirable medical occurrence/adverse drug experience that at any dose:

- results in death (any cause, except progression of cancer under study)
- is life-threatening
- requires or prolongs inpatient hospitalisation (see 11.4.1 for details)
- results in persistent or significant disability/incapacity
- constitutes an important medical event
- is a congenital anomaly or birth defect (including neonatal deaths and abortions)
- is a secondary malignancy/second primary malignancy

11.4.1. Inpatient hospitalisation

A hospital stay equal to, or greater than, 24 hours. Hospitalisations occurring under the following circumstances are **not** considered to be SAEs:

- elective surgery, for pre-existing conditions and planned prior to trial entry
- occur on an outpatient basis and do not result in admission (hospitalisation <24h)
- are part of the normal treatment or monitoring of the studied treatment

11.4.2. Important medical events

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalisation, or disability, but may jeopardise the patient or require medical or surgical intervention to prevent one of the other outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

11.4.3. Secondary malignancies / second primary malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

A second primary malignancy is one that is unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

SAEs are required to be reported to ETOP immediately (i.e., within 24 hours after awareness of the event) by completing the SAE eCRF (*SAE Initial Reports*). See Section 11.12 for detailed reporting instructions.

11.5. Pregnancy

Patients who are not of childbearing potential due to being postmenopausal (2 years without menstruation) or surgical sterilisation (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for the trial. All other patients are considered to be of childbearing potential and must use adequate contraception throughout the trial.

Women of childbearing potential and sexually active men must use highly effective contraception during trial treatment and until at least 3 months thereafter. Please refer to Section 10.6.1 for highly effective contraception methods.

11.5.1. Abortions

Any abortion (miscarriage, spontaneous, induced or elective abortion) should be classified as an SAE (as the ETOP as the sponsor considers abortions to be medically significant) and reported to ETOP immediately (i.e., within 24 hours after awareness of the event) by completing the SAE eCRF (***SAE Initial and Follow-up Reports***).

11.5.2. Congenital anomalies/birth defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to IMP or the female partner of a male patient exposed to the IMP should be classified as an SAE and reported to ETOP immediately (i.e., within 24 hours after awareness of the event) by completing the SAE eCRF (***SAE Initial and Follow-up Reports***).

11.5.3. Maternal exposure

In the case of pregnancy occurring during the course of the trial or within at least 3 months after treatment discontinuation, the investigator shall immediately (within 24 hours after awareness of pregnancy) notify ETOP by completing the ***pregnancy eCRF*** in ETOPdata in accordance with the SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported (within 14 days) by submitting a second ***pregnancy eCRF*** in ETOPdata. All neonatal deaths and

congenital anomalies/birth defects that occur within 30 days of birth should be reported, irrespective of causality, as SAEs. In addition, any infant death after 30 days, irrespective of causality should also be reported within 24 hours of the investigator's knowledge of the event using the *SAE eCRF*.

11.5.4. Paternal exposure

Pregnancy that occurs in a female partner of a male trial participant is not considered to be an adverse event. The pregnant partner will need to sign a "Pregnant Partner ICF" to allow for follow-up on her pregnancy.

The outcome of all pregnancies (spontaneous abortion or miscarriage, induced or elective abortion, ectopic pregnancy, normal birth or congenital abnormality) must immediately be reported (within 24 hours after awareness of pregnancy) to ETOP by completing the ***pregnancy eCRF*** in ETOPdata in accordance with the SAE reporting procedures. .

11.6. Exceptions to the SAE definition

The following situations do not need to be reported as SAEs:

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalisation which was planned before the patient consented for trial participation and where admission did not take longer than anticipated (see also 11.4.1).
- A hospitalisation planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (serious) AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen significantly.
- Progression or death due to worsening of cancer under study (see Section 11.6.1 for details).

11.6.1. Deaths

For the ALERT-lung protocol, mortality is a secondary efficacy endpoint. Deaths that occur during the protocol-specified adverse events reporting period (e.g. during trial treatment and within 30 days following cessation of treatment) that are attributed by the investigator solely to progression of the underlying disease should be recorded on the ***End of Treatment eCRF*** and ***the Follow-up eCRF***.

All other on-trial deaths, regardless of relationship to IMP, must be recorded on the SAE eCRF (***SAE Initial and Follow-up Reports***) and immediately (within 24 hours) reported to ETOP.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE eCRF (***SAE Initial and Follow-up Reports***). Generally, only one such event

should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.

If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the SAE eCRF (***SAE Initial and Follow-up Reports***).

If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

11.7. Adverse events of special interest (AESI)

The following events of special interest (AESI) are not necessarily SAEs, but should be reported as such on the SAE eCRFs (***SAE Initial Reports***) by indicating that this is an "adverse event of special interest".

AESIs are required to be reported to ETOP immediately (i.e., within 24 hours after awareness of the event) by completing the SAE eCRF (***SAE Initial Reports***). See Section 11.12 for detailed reporting instructions.

AEs of special interest for this trial are the following:

11.7.1. Drug-induced liver injury

Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.

The finding of an elevated ALT or AST (>3× baseline value) in combination with either an elevated total bilirubin (>2× ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report the occurrence of either of the following:

- Treatment-emergent ALT or AST >3× baseline value in combination with total bilirubin >2× ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST >3× baseline value in combination with clinical jaundice

The most appropriate diagnosis or the abnormal laboratory values, if a diagnosis cannot be established, should be recorded.

11.7.2. Suspected transmission of an infectious agent by the IMP

Suspected transmission of an infectious agent by the IMP as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

11.7.3. Adverse events associated with an overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of IMP is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of the IMP are required to be reported to ETOP immediately (i.e., within 24 hours after awareness of the event) by completing the SAE eCRF, whether the event fulfils "serious" criteria or not.

11.8. Severity / intensity of (serious) adverse events

The (serious) AE severity grade provides a qualitative assessment of the extent or intensity of a specific event, as determined by the investigator or as reported by the patient. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to trial drug. A severe event may be of relatively minor medical significance (such as severe headache). The term "severe" is **not** the same as "serious", which is based on patient/event **outcome** or **action criteria** associated with events that pose a threat to a patient's life or functioning.

Severity grade for other adverse events not covered in the toxicity grading scale:

- **Grade 1** = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- **Grade 2** = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- **Grade 3** = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisation is possible
- **Grade 4** = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable
- **Grade 5** = Death – the event results in death

11.9. Causality of adverse events

The investigator must determine the relationship between the administration of trial drug(s) and the occurrence of an AE/SAE following the definitions indicated below:

Not suspected	The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected	The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Relationship to the protocol treatment	
Not suspected	**Suspected / related to trial treatment**
- unrelated - unlikely	- possible - probable - definite

11.10. Duration of adverse events

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

11.11. Action taken

The investigator will report the action taken with trial drug(s) because of an AE or SAE, as applicable (e.g. discontinuation of trial drug(s), medication needed for the treatment of an AE) and in case of an SAE report if concomitant and/or additional treatments were given for the event.

11.12. Reporting of adverse events

11.12.1. Reporting of adverse events

All AEs, regardless of relationship to IMP, will be reported from the date of signature of informed consent until 30 days after the last dose of IMP. After this period, the investigator is not required to actively monitor patients for AEs; however, ETOP should be notified if the investigator becomes aware of any post-study SAEs or AESIs that are at least possibly related to previous trial treatment.

During trial treatment and until 30 days after the last dose of IMP, investigators should seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by trial personnel, will be recorded in the patient's medical record and on the ***Adverse Event eCRF***.

11.12.2. Reporting of serious adverse events

Any SAE, whether related to alectinib or not, or any AESI will be reported from the date of signature of informed consent until 30 days after the last dose of IMP. Information about all such events will be collected and recorded on the SAE eCRFs (***SAE Initial and Follow-up Reports***).

After completion of trial treatments, report all SAEs beyond 30 days that are considered at least possibly related to previous trial treatment. Cases of secondary malignancies and congenital abnormalities and neonatal deaths are to be considered as SAEs, regardless of whether they occur during or after trial treatment. These events should be reported during the whole trial duration on the serious adverse event eCRFs (***SAE Initial and Follow-up Reports***)

To ensure patient safety, ETOP must be informed of each SAE using the procedures described below:

- Any SAE must be reported by submitting the completed ***SAE Initial Reports*** eCRF in English within 24 hours of awareness in the EDC system ETOPdata.

- Queries may be issued by the ETOP safety office; a timely response by the investigator to all SAE-related queries is crucial.
- The SAE outcome must be reported within 15 days after initial reporting by online submitting the ***SAE Follow-up Report*** **eCRF**. In case the SAE is reported as ongoing after 15 days, a second follow-up report has to be submitted with the final outcome.

Submission of SAE is done via the EDC system, or in case of unavailability, by sending the SAE form by fax to the ETOP safety office:

+41 31 389 92 29

As soon as the EDC system is available again, the SAE eCRF has to be completed and submitted by the site.

The ETOP safety office will inform Roche safety and other appropriate persons about all SAEs within 24 hours of receipt at the ETOP safety office.

The ETOP safety office will review the SAE and prepare a summary report of all SAEs received. Listings of SAEs will be prepared as required.

The ETOP safety office will assess serious adverse events for expectedness. Any unexpected serious adverse reactions (SUSARs) occurring in this trial qualify for expedited reporting and ETOP will notify the appropriate regulatory authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

11.13. Reference safety information

For the determination of the expectedness of the serious adverse events of alectinib, Section 6 of the most recent version of the ***Alectinib IB*** serves as reference safety information

The Sponsor will compare the severity of each event for the trial with the severity in the applicable reference document.

12. Response evaluation

12.1. CT schedule for response evaluation

All patients must have a contrast enhanced CT thorax and upper abdomen (from top of thorax until adrenal glands and full liver and kidneys included) at baseline during screening within 6 weeks before enrolment. CT scan will be repeated 8 weeks (±4 days) after first dose of alectinib and then every 8 weeks (±4 days) until disease progression.

The same imaging technique, acquisition, and processing parameters should be used in a patient throughout the trial.

In the case that a CT scan had to be done earlier or later than scheduled, effort should be made to return to the original CT schedule.

12.2. Storage of images for central review

All CT images must be stored locally in electronic format for later central review, please consult the ***ALERT-lung Procedures Manual*** for details.

Any information from which the identity of patients could be deduced must be removed before transferring any imaging data for central review (e.g. initials, birth date etc.).

12.3. Response evaluation criteria in solid tumours (RECIST version 1.1)

12.3.1. Introduction

All included patients will be evaluated for disease response and progression according to the revised response evaluation criteria in solid tumours (RECIST version 1.1)[16]

In this trial, patients must have **measurable or evaluable** disease (see definitions below).

12.3.2. Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumour effect of a treatment.

CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. CT scan should generally be performed using a ≤5 mm contiguous reconstruction algorithm. MRI is acceptable for certain situations, e.g. body scans.

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules) and ≥10 mm. In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scan is preferable.

Ultrasound is not useful in assessment of lesion size and is not accepted as a method of assessment.

FDG-PET is not foreseen for regular response assessments. It may, however, be used to detect or confirm the appearance of new lesions. Attenuation correction CT scans performed as part of a PET/CT scan frequently show lower resolution; therefore, dedicated CT scans are preferred. However, if the site can demonstrate that the CT scan performed as part of a PET/CT is of the same diagnostic quality as a diagnostic CT scan (with *i.v.* and oral contrast), then the CT scan portion of the PET/CT can be used for RECIST measurements.

12.3.3. Non-measurable disease

Non-measurable disease is defined as lesions or sites of disease that cannot be measured. Non-measurable lesions/sites of disease and special considerations:

- Small non-nodal lesions (longest diameter <10 mm in CT scan)
- Small lymph nodes (short axis ≥10 and <15 mm). Lymph nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed as measurable or non-measurable disease.

- Bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.
- Leptomeningeal disease
- Ascites
- Pleural or pericardial effusion
- Lymphangitic involvement of skin or lung
- Cystic lesions. Cystic lesions thought to represent cystic metastases may be considered as measurable lesions. However, if non-cystic lesions are present, these are preferred as target lesions
- Tumour lesions situated in a previously irradiated area, or subjected to other locoregional therapy. Such lesions may be considered measurable if there has been demonstrated progression in the lesion
- Abdominal masses/abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques

12.3.4. Measurable disease

Measurable disease is defined as the presence of at least one measurable lesion.

Measurable lesions:

- Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5mm)
  - 10 mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable)
  - 20 mm by chest X-ray

  Reminder: A lesion in a previously irradiated area is not eligible for measurable disease.
- **Malignant lymph nodes**: to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan, assuming the slice thickness is ≤5 mm. At baseline and in follow-up, only the short axis will be measured.

12.3.5. Selection of target lesions

Target lesions should be identified, measured and recorded at baseline. At baseline, there can be up to a maximum of 5 lesions representative of all involved organs, and up to 2 per organ. Target lesions should be selected on the basis of their size and their suitability for accurate repetitive measurements. A sum of diameters for all target lesions will be calculated and reported as the baseline sum of diameters. **Lymph nodes** selected as target lesions should always have the **short axis** recorded. All **other lesions** should always have their **longest**

diameters recorded. The sum of diameters will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease.

12.3.6. Selection of non-target lesions

All other lesions (or sites of disease) not identified as target lesions should also be recorded as non-target lesions at baseline.

For non-target lesions, measurements are not required, but the presence or absence of each should be noted throughout follow-up. It is possible to record multiple non-target lesions as a single item on the eCRF.

12.3.7. Evaluation of target lesions

All target lesions will be measured at each tumour assessment, and the sum of their diameters will be compared to previous assessments in order to assign the response status as specified below.

- Complete Response (CR): Disappearance of all target lesions. Lymph nodes selected as target lesions must each have reduction in the short axis to <10 mm in order for the response to be considered complete. In this case, the sum of diameters may be >0.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.
- Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on the trial. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions (see Section 12.3.9) denotes disease progression.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on the trial.

Note: All target lesions, including lymph nodes, should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist does not feel comfortable assigning an exact measure and reports a lesion as "too small to measure", a default value of 5 mm should be recorded. If a target lesion is thought likely to have disappeared, use "0 mm."

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

12.3.8. Evaluation of non-target lesions

- Complete Response (CR): Disappearance of all non-target lesions; lymph nodes selected as non-target lesions must be non-pathological in size (<10 mm).
- Non-CR/non-PD: Persistence of one or more non-target lesions (non-CR).

- Progression (PD): unequivocal progression of existing non-target lesions. Unequivocal means: comparable in magnitude to the increase that would be required to declare PD for measurable disease or an overall substantial increase in tumour burden that merits treatment discontinuation.

When no imaging is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesions are evaluated at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

12.3.9. Determination of new lesions

The appearance of any new malignant lesion denotes disease progression. The finding of a new lesion should be unequivocal, i.e. not attributable to differences in scanning technique or findings thought to represent something other than tumour. If a new lesion is equivocal, e.g. because of its small size, the patient will stay on treatment (if the decision on PD is based on this lesion only). If the repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the previous scan when the lesion was discovered.

Lesions or sites of disease found in a new location not included in the baseline scan (e.g. brain metastases) are considered new lesions. The detection of new lesions is not restricted to the examination methods used at baseline.

Note: the "re-appearance" of a previously "disappeared" target or non-target lesion does not in itself necessarily qualify as PD; this is the case only if the overall evaluation meets the PD criteria, or if the patient was previously in CR.

12.3.10. Additional considerations

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.3.11. When the patient has only non-measurable disease

This circumstance arises in some phase III trials when it is not a criterion of trial entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable).

A useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e.an increase in tumour burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion).

Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localised to widespread. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II of reference. [16]

If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

12.3.12. Determination of time point response

Based on the responses of target lesions, non-target lesions, and the presence or absence of new lesions, the overall response will be determined at each tumour evaluation time point, according to the table below.

12.3.13. For patients with measurable disease

Table 3: Measurable Disease - Overall Response

Target lesions	**Non-target lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR / non-PD*	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*Non-CR/non-PD should be used rather than SD for categorizing non-target lesions.

12.3.14. For patients with non-measurable disease

Table 4: Non-measurable Disease - Overall Response

Non-target lesions	**New lesions**	**Overall response**
CR	No	CR
Non-CR / non-PD*	No	Non-CR / non-PD*
Not evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

*Non-CR/non-PD should be used rather than SD for categorizing non-target lesions.

12.3.15. Determination of best overall response

Best overall response is defined as best response recorded from the start of trial treatment across all time points until the end of trial treatment.

13. Endpoints definition

13.1. Overall response

Overall response, the primary endpoint, is defined as best overall response (complete response (CR) or partial response (PR) according to RECIST criteria v1.1 (see Section 12.3) from the start of trial treatment across all time points until the end of trial treatment.

13.2. Disease control

Disease control (DC) is defined as complete or partial response, or disease stabilisation at 24 weeks.

13.3. Progression-free survival

PFS is defined as the time from the date of enrolment until documented progression (based on RECIST 1.1 criteria) or death, if progression is not documented. Censoring (for patients without a PFS/death event) will occur at the last tumour assessment if patient is lost to follow-up or refuses further documentation of follow-up.

13.4. Overall survival

OS is defined as time from the date of enrolment until death from any cause. Censoring will occur at the last follow-up date.

13.5. Toxicity

All safety parameters will be summarised in tables to evaluate the safety profile of patients treated with alectinib in terms of:

- Adverse events including adverse events leading to dose modifications or interruptions, study drug withdrawal, and death
- Severe, serious, and selected adverse events
- Deaths
- Laboratory parameters and abnormalities, vital signs and ECGs

Adverse events will be coded using MedDRA and summarized by mapped term and appropriate thesaurus level. All adverse events and routine laboratory parameters will be assessed according to the NCI CTCAE v4.0 grading system. For adverse events, the most extreme intensity will be used for reporting. Adverse events will be described by individual listings and by body system, as well as by severity. In tables showing the overall incidence of adverse events, patients who experienced the same event on more than one occasion are

counted only once in the calculation of the event frequency. Laboratory values will be summarized including summary tables for the shifts in grades from baseline to the worst grade observed during treatment. Descriptive summary tables of change from baseline over time will be provided for vital signs. ECG findings over time will be summarized. Study drug administration will be summarized by duration and cumulative dose. In addition, treatment exposure will be summarized including the number of doses received, dose intensity, and the percentage of planned dose.

14. Biological material and translational research

14.1. Biomarker program

The biomarker program has the following goals:

- Identification of the translocation-partners of RET
- Investigation of mechanisms for intrinsic and acquired resistance
- Identification of co-occurring mutations in the initial FFPE-material by parallel-sequencing
- Search for potential mechanisms of resistance upon progression
- Investigate test characteristics of FISH as current gold-standard compared to parallel-sequencing or Nanostring technology.
- Development of diagnostic assays

14.2. Biobank

A central biobank with all biological material collected from every patient enroled in this trial will be established for translational research, which is integral to the trial. The required pathology material (described below) is submitted to, catalogued, and maintained at the **ALERT-lung Central Laboratory**, located at the Institute for Pathology, **University Hospital Cologne, Germany**. Formalin-fixed, paraffin-embedded (FFPE) tumour tissue blocks (tissue blocks, resection or biopsy specimen) or cytoblocks collected prior to treatment with alectinib, will be centrally collected and biobanked at the central laboratory in Cologne. The material will undergo central histology review, investigation of RET using FISH and parallel-sequencing of cancer-related genes. Upon progression, a re-biopsy of the progressive lesion is strongly encouraged to obtain fresh-frozen biopsy material for whole-exome sequencing. An EDTA-blood sample at progression, which can be taken in the same setting as the biopsy at progression, is required as a matched reference normal DNA sample.

14.3. Central RET confirmation

RET rearrangement of tumour samples from all enroled patients will be retested by FISH and by parallel-sequencing at the Central Laboratory in Cologne. In the routine clinical setting, FISH is currently the gold-standard to detect RET-rearrangements. However, the technique has limited sensitivity and specificity. Thus, comprehensive parallel-sequencing will be used to determine the sequence of the rearrangement and to compare it with the FISH-patterns. Parallel-sequencing will also allow the determination of potential co-occurring mutations and the translocation-partner of RET, both of which have potential clinical implications.[5]

14.4. Diagnostic assay development

In the current age of targeted therapies, advances in biomarker identification and the increasing access to biomarker testing have allowed for a more personalised healthcare approach and treatment with appropriately targeted therapies. However, these technological advances have also helped to uncover some limitations to be overcome in order for truly personalised healthcare to become a reality.

The first of these limitations is that for many patients with tumours like NSCLC, obtaining enough tissue to test for an ever-increasing number of biomarkers is difficult. This in effect limits diagnostic testing, the associated targeted drug development, and thus, treatment options for patients.

Further, retesting patients multiple times throughout the course of therapy to guide treatment is rarely possible, as the benefit-risk ratio of obtaining more tissue is often not favourable.

A second limitation is that some tumours considered common, such as NSCLC, are increasingly being divided into subgroups based on infrequently or rarely occurring biomarkers. A more efficient means to test patients and develop drugs targeted at identified mutations or biomarkers is needed in order to provide these patients with access to effective and innovative treatment options.

> A multiplex diagnostic test based on easily accessible substrate such as circulating cell-free DNA (cfDNA) from blood would allow the testing of more samples to determine their molecular status and would therefore contribute significantly to providing the most appropriate molecularly based treatment option for each patient.

14.5. Mandatory biomaterial

- FFPE tumour block from a biopsy or resection prior to treatment with alectinib must be centrally submitted. Suitable materials are any biopsy or resection specimens as well as cytoblocks.
- Pathology Report from biopsy after disease progression on the most recent treatment regimen prior to treatment with alectinib (all information allowing identification of the patient, e.g. patient name, day and month of birth, must be removed).
- 2x 5 mL tubes of plasma for diagnostic assay development, from 20 mL whole blood, immediately frozen at -80°C in EDTA blood tubes and stored locally at -80°C until further notice. Please consult the A**LERT-lung Procedures Manual** for details.

14.6. Biomaterial at progression

Upon progression of the disease, the following biomaterial is collected:

- 2x 5 mL tubes plasma for translational research, from 20 mL whole blood, immediately frozen at -80°C in EDTA blood tubes and stored locally at -80°C until further notice.

Patients should also be encouraged to have a re-biopsy of the progressive lesion with the aim of performing whole-exome sequencing (WES). If the patient agrees to a re-biopsy procedure, a whole blood sample should also be collected and a pathology report submitted:

- Fresh frozen re-biopsy
- Whole blood sample (9-10 mL) to be taken at the time of re-biopsy
- Pathology Report from biopsy at progression (all information allowing identification of the patient, e.g. patient name, day and month of birth, must be removed).

The re-biopsy material should be snap-frozen in liquid nitrogen upon extraction and stored locally at (-80°C). The 2x 5 mL plasma and the 9-10 mL whole blood samples should stored in EDTA tubes and stored locally at 80°C.

Both samples will be shipped to the central laboratory at the end of the trial. The re-biopsy material will undergo histological review. If sufficient material is available, WES will be performed to detect potential mechanisms of resistance. The whole EDTA-blood will be used to extract genomic DNA (non-tumour) as reference. This analysis is for scientific purposes only and will not be used for clinical-decision making.

14.7. Submission of biomaterial

All biological samples collected during the conduct of the trial must be marked with the ETOP patient identifier issued by the EDC system and registered in the ETOP system.

Anonymised pathology reports should be uploaded via the EDC system. Please consult the ***ALERT-lung Procedures Manual*** for specific instructions on how to submit the samples and pathology reports.

15. Trial procedures

This section gives an overview of procedures, clinical and laboratory evaluations and follow-up investigations.

15.1. Tumour assessment

Radiological tumour assessment by CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) will be done as indicated in Section 12.1 until PD.

15.2. Baseline evaluations

The following examinations should be done within 28 days before enrolment.

Written informed consent:

Before any trial specific evaluations or interventions (within 6 weeks prior enrolment).

15.2.1. Medical history:

Including smoking history, medications, comorbidities, allergies and baseline symptoms. Baseline symptoms will be recorded on the adverse events form.

15.2.2. Physical examination:

According to local standards, including performance status, heart rate, and temperature, blood pressure and body weight.

15.2.3. Chemistry

CPK, sodium, potassium, calcium, magnesium, phosphate, glucose.

15.2.4. Haematology

WBC, haemoglobin, platelets, neutrophils.

15.2.5. Hepatic function

ALT, AST, AP, bilirubin, GGT, LDH.

15.2.6. Renal function

Serum creatinine, creatinine clearance (Cockcroft-Gault).

15.2.7. Urine analysis on first morning urine sample (microscopic urine analysis or dipstick)

pH, proteins, glucose, blood.

15.2.8. Electrocardiogram

15.2.9. Pregnancy test

Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine beta-HCG pregnancy test within 7 days before enrolment into the trial and within 3 days before alectinib

treatment start. Pregnancy testing has to be repeated during the duration of the trial treatment according to local standard.

15.2.10. Brain MRI or contrast enhanced CT, performed within 6 weeks before enrolment.

15.2.11. Radiological tumour assessment

By CT scan of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included), performed within 6 weeks before enrolment.

15.2.12. TNM categories

15.2.13. FFPE tumour material

15.2.14. Plasma sample

15.3. Evaluations at every treatment visit

Treatment has to start as soon as possible after enrolment, ideally within 7 days. Treatment visits are planned at treatment start (week 0) and then every 2 weeks (±3 days) for the first 12 weeks and every 4 weeks (±3 days) thereafter. The following evaluations should be done within 24 hours of every treatment visit.

15.3.1. Patient diary

Patient diary should be checked and capsules returned should be counted.

15.3.2. Physical examination:

According to local standards, including performance status, heart rate, and temperature, blood pressure and body weight.

15.3.3. Recording of symptoms, adverse events and concomitant medications:

Adverse events have to be reported on the adverse event form, from the date of signature of informed consent until 30 days after trial treatment discontinuation.

15.3.4. Chemistry

Sodium, potassium, calcium, magnesium, phosphate, glucose will be repeated if clinically indicated according to local standards.

15.3.5. CPK has to be measured only at treatment visit 1, 2 and 3 (week 0, 2 and 4) and then repeated if clinically indicated.

15.3.6. Haematology

WBC, haemoglobin, platelets, and neutrophils will be repeated if clinically indicated according to local standards.

15.3.7. Hepatic function

ALT, AST, AP, bilirubin, GGT, LDH

15.3.8. Renal function

Serum creatinine, creatinine clearance (Cockcroft-Gault) will be repeated if clinically indicated according to local standards.

15.3.9. Urine analysis on spot urine (microscopic urine analysis or dipstick)
pH, proteins, glucose, blood will be repeated if clinically indicated according to local standards.

15.3.10. Radiological tumour assessment as indicated in Section 12.1.

15.4. Evaluations at disease progression

At progression, the following assessments are required:

15.4.1. Radiological tumour assessment
By CT scan of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included)

At progression, collection of the following samples for translational research is encouraged:

15.4.2. Fresh frozen re-biopsy

15.4.3. Plasma sample

15.4.4. Whole blood in EDTA tube

15.5. Evaluations under treatment beyond progression

In case of clinical benefit, with physician and patient agreement, trial treatment can continue beyond confirmed progression for as long as the patient may still derive benefit as per investigator decision. The following evaluations should be done within 24 hours of every treatment visit.

15.5.1. Patient diary
Patient diary should be checked and capsules returned should be counted.

15.5.2. Physical examination:
According to local standards, including performance status, heart rate, and temperature, blood pressure and body weight.

15.5.3. Recording of symptoms, adverse events and concomitant medications:
Adverse events have to be reported on the adverse event form, from the date of signature of informed consent until 30 days after trial treatment discontinuation.

15.5.4. Chemistry
Sodium, potassium, calcium, magnesium, phosphate, glucose will be repeated if clinically indicated according to local standards.

15.5.5. CPK has to be measured only at treatment visit 1, 2 and 3 (week 0, 2 and 4) and then repeated if clinically indicated.

15.5.6. Haematology

WBC, haemoglobin, platelets, and neutrophils will be repeated if clinically indicated according to local standards.

15.5.7. Hepatic function

ALT, AST, AP, bilirubin, GGT, LDH

15.5.8. Renal function

Serum creatinine, creatinine clearance (Cockcroft-Gault) will be repeated if clinically indicated according to local standards.

15.5.9. Urine analysis on spot urine (microscopic urine analysis or dipstick)

pH, proteins, glucose, blood will be repeated if clinically indicated according to local standards.

15.6. Evaluations at the end of treatment visit

At the end of trial treatment and irrespective of the reason for stopping treatment, an end of treatment visit at the centre is to be scheduled within 30 days following the decision to stop trial treatment or within 30 days after planned treatment start if treatment never started. In case treatment was delayed due to AEs and could not be resumed (for example if treatment interruption exceeded 21 consecutive days), the end of treatment visit should be performed within 8 weeks after the last dose.

15.6.1. Patient diary

Patient diary should be checked and capsules returned should be counted.

15.6.2. Physical examination:

According to local standards, including performance status, heart rate, and temperature, blood pressure and body weight.

15.6.3. Recording of symptoms, adverse events and concomitant medications:

Adverse events have to be reported on the adverse event form, from the date of signature of informed consent until 30 days after trial treatment discontinuation.

15.6.4. Chemistry

Sodium, potassium, calcium, magnesium, phosphate, glucose.

15.6.5. CPK if clinically indicated.

15.6.6. Haematology

WBC, haemoglobin, platelets, neutrophils

15.6.7. Hepatic function

ALT, AST, AP, bilirubin, GGT, LDH

15.6.8. Renal function

Serum creatinine, creatinine clearance (Cockcroft-Gault).

15.6.9. Urine analysis on first morning urine sample (microscopic urine analysis or dipstick)
pH, proteins, glucose, blood

15.6.10. Electrocardiogram

15.6.11. Radiological tumour assessment
By CT scan of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included), repeated if not done within 6 weeks prior to end of treatment visit

15.7. Evaluations in the follow-up phase (post treatment) before progression

Patients who discontinue trial treatment before progression should have the following examinations documented every 8 weeks (±4 days), aligned with the imaging visits.

15.7.1. Recording of symptoms, adverse events and concomitant medications:
Adverse events have to be reported on the adverse event form, from the date of signature of informed consent until 30 days after trial treatment discontinuation.

15.7.2. Radiological tumour assessment
By CT scan of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included)

15.7.3. Survival

15.8. Evaluations in the follow-up phase beyond progression of disease

Patients with progression that ends trial treatment will be followed up every 12 weeks (±2 weeks) starting from date of progression until trial end (e.g. until 6 months after inclusion of the last patient). They should have documented:

15.8.1. Further lines of treatment

15.8.2. Survival

16. Case report forms and documentation

16.1. Case report forms schedule

eCRFs will only be available on-line at the electronic data capture (EDC) facility ETOPdata. No paper forms will be used, with the exception of a paper SAE form and pregnancy form in case of system unavailability.

Table 5: Case report forms:

eCRF in ETOPdata	**To be completed**
1 - Eligibility Check and Enrolment	Within 28 days of start of baseline evaluations
2 - Baseline	Within 14 days after enrolment
3 - Tumour Assessments	Baseline before enrolment: within 14 days after enrolment; During trial until tumour progression: within 14 days of date of each radiological imaging.
4 - Concomitant Medications	Continuously from date of enrolment to 30 days after end of trial treatment; - within 14 days after enrollment - within 14 days after each treatment visit - within 14 days after End of treatment visit or within 14 days after Follow-up visits.
5 – Alectinib Treatment Visit	Within 14 days after each alectinib treatment visit.
6 - Adverse Events	Continuously from date of Informed Consent signature to 30 days after all treatment discontinuation; - within 14 days of enrolment (baseline symptoms) - within 14 days of start of each treatment visit - within 14 days after End of Treatment visit or within 14 days of Follow-up visits.
7 - Serious Adverse Event Initial Reports	Within 24h of awareness of SAE; All SAEs and AESIs must be submitted via ETOPdata, submission via fax to ETOP safety office only in case of unavailability of ETOPdata.
8 - Serious Adverse Event Follow-up Reports	Within 15 days of completion of initial report. If event was not resolved after 15 days, submit an additional report within 7 days of resolution of event.
9 - End of Treatment	Within 14 days after End of Treatment visit.

eCRF in ETOPdata	To be completed
10 - Follow-up	Within 14 days of follow-up visits, which take place: Before progression: every 8 weeks (+/-4 days), coinciding with imaging visits; After progression: every 12 weeks (+/-2 weeks) from date of progression until trial end; On death: Within 14 days upon awareness of death
11 - Pregnancy	Maternal exposure: Within 24h of first documentation of pregnancy; Within 14 days of end of pregnancy. Paternal exposure (pregnancy in a female partner of a male trial participant): At end of pregnancy.
12 – WC/LFU	Within 14 days of awareness of withdrawal of consent or loss to follow-up.
13 - Biological Material Tracking	This eCRF is to be completed incrementally. Entries are to be made: - within 14 days of enrolment: for information pertaining to "FFPE Tumour tissue: at enrolment" (prior to treatment with alectinib); - immediately after local storage of blood samples (on same day): for information pertaining to "Blood samples: at progression"; - within 14 days of progression: for information pertaining to "Fresh-frozen Tumour tissue: at progression" (after trial treatment, optional); - immediately (on same day) after submission of material (FFPE, fresh-frozen tumour tissue and blood) for central biobanking: for "Date Specimen sent to Central Lab".

17. Statistical considerations

17.1. Primary objective

The primary objective of this single arm phase II trial is to assess the efficacy of alectinib in terms of best overall response (OR) assessed by RECIST 1.1, for patients with pretreated RET-rearranged advanced NSCLC.

17.2. Sample size determination

The target population of this trial includes patients with advanced stage RET-rearranged NSCLC, treated with at least one platinum based systemic chemotherapy regimen.

A best OR rate of 35% is targeted, while an OR rate of 15% is considered to be too low.

Based on a one-sided exact test for proportions, the trial is designed to test the null hypothesis H_0: p0 ≤0.15 versus the alternative HA: pA >0.35, where p is the rate of OR (ORR) at a one-sided significance level of 0.025 and a power of at least 0.80.

The attained alpha of 0.015 and power of 82% are achieved with a sample size of 41 evaluable patients. The null hypothesis H_0 will be rejected and the alternative hypothesis H_1 accepted if at least 12 patients achieve OR.

A total sample size of 44 patients is required, allowing for up to 3 patients to be replaced if a patient is ineligible (retrospective review), has not started the experimental treatment or is lost to follow-up before the first confirmed response evaluation, according to RECIST 1.1.

17.3. Trial duration

Clinical visits are expected to span approximately 44 months after enrolment of the first patient, assuming an accrual rate of approximately 1 patient per month and a start-up period of 6 months as the trial is activated by participating centres.

The trial ends when both of the following criteria are satisfied:

- The trial is mature for the analysis of the primary endpoint, according to protocol specifications.
- The cleaning procedure of the database is completed and database is ‘frozen’.

The total duration of the trial is expected to be 5 years, including a run-in period of 6 months and an additional 6 months for the final analysis report.

17.4. Analysis populations

17.4.1. Intention-To-Treat Cohort

The Intention-To-Treat (ITT) cohort will include all patients enroled in the trial.

17.4.2. Efficacy Cohort

The efficacy cohort will encompass all evaluable patients, e.g. all enroled 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).

17.4.3. Safety Cohort

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

17.5. Evaluation of primary and secondary objectives

The primary analysis of OR will be performed on all the patients included in the efficacy cohort. OR rate will be estimated along with the corresponding 95% exact binomial confidence interval (CI).

The secondary time-to-event endpoints (PFS and OS), evaluated on the efficacy cohort, will be estimated by the Kaplan-Meier method. Kaplan-Meier plots will be presented, median survival estimates and estimates of the event-free rate at fixed time points and 95% CIs will also be obtained using the Kaplan-Meier technique.

Clinical efficacy will be further explored by the estimation of disease control rate (DCR) and its corresponding 95% exact binomial confidence interval.

Median follow-up time will be estimated based on the reverse censoring method.

A secondary analysis of the efficacy endpoints evaluated for all patients in the ITT cohort will also be performed.

The safety and the tolerability of the trial treatment will be evaluated by the occurrence of AEs on all patients that have received at least one dose of trial treatment (safety cohort). Classification of severity and causality will be performed according to CTCAE v4.0 and will be presented using tables and bar charts. For each subject, each AE will be analysed according to the worst grade of toxicity observed over the whole treatment period.

Further exploratory analyses include description of primary and secondary outcomes for patient subgroups of interest, as defined by patient or tumour characteristics or different levels of biomarkers examined.

More detailed description of the statistical analysis for the primary and secondary endpoints as well as for the translational research will be provided in the corresponding Statistical Analysis Plan (SAP) document.

17.6. Safety evaluation

Safety evaluations of the trial treatment will be performed twice per year and presented for review to the ETOP Independent Data Monitoring Committee (IDMC) at each of their bi-annual meetings. Recruitment into the trial will continue while safety is being evaluated.

17.7. Interim efficacy analysis

No formal interim efficacy analysis is planned in the framework of this trial.

18. Criteria for termination of the trial

18.1. General criteria for termination of the trial

The trial may be discontinued early in parts or completely if the information on the IMPs leads to doubt as to the benefit/risk ratio, by decision of the ETOP Foundation Council upon recommendation of the ETOP 12-17 ALERT-lung Steering Committee and IDMC. Specific considerations will be based on the regular safety reviews by the ETOP IDMC.

The trial can be terminated at any time if the authorization and approval to conduct the trial is withdrawn by ethics committee or regulatory authority decision, insufficient accrual, emerging new data impacting the scientific value of the trial or ethical grounds.

18.2. Discontinuation of protocol treatment for individual patients

Protocol treatment should be stopped in the following situations:

- Disease progression according to RECIST criteria 1.1.
- Occurrence of unacceptable toxicities. Stopping protocol treatment is determined by medical judgment of the treating physician.
- Request by the patient. Patients have the right to refuse further trial treatment at any time during the trial. Such patients will remain in the trial and will be transferred to the follow-up phase.
- If a patient refuses to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective.

The decision for discontinuation of protocol treatment of individual patients is taken by the treating physician based on her/his medical evaluation and taking into account the patient's individual situation.

18.3. Withdrawal of consent

Patients have the right to withdraw consent for further trial participation at any time without having to specify the reason. The data recorded up to the time point of withdrawal will continue to be evaluated in the trial. The investigator should ask the patient for consent to continue to collect information on her/his disease and survival status.

It should be documented in both the medical records and in the eCRF, according to the instructions in the ***ALERT-lung CRF Completion Guidelines***, if the patient accepts to be contacted for survival status despite withdrawing the trial consent. For the patient's safety, an end of treatment visit should be performed and documented in the eCRF if the patient agrees to this.

19. Ethics aspects, regulatory approval, and patient informed consent

The investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice (GCP)" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

19.1. Ethical Review Board/Ethics Committee

All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The ERB/IRB decision must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent.

The Ethical Review Board/Institutional Review Board (ERB/IRB) written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent. Documentation of Ethics Committee approval must be sent to the ETOP coordinating office prior to enrolment of the first patient.

Any modifications made to the protocol must be submitted to the appropriate ERB/IRB for information or approval in accordance with local procedures and regulatory requirements and to health authorities if required.

Once approved or acknowledged by the appropriate ERB/IRB and by the health authorities (if required), the investigator shall implement the protocol modifications. Protocol modifications for urgent safety matters may be directly implemented following the instructions of ETOP.

19.2. Regulatory approval procedures

If applicable, in addition to the approval of the ethics committee according to national legislation, the protocol, protocol related documents including patient information and informed consent and other documents as required locally must be submitted to and be approved by the health authority. Documentation of health authority approval must be sent to the ETOP coordinating office prior to participating centre activation.

19.3. Informed consent

Informed consent for each patient will be obtained prior to initiating any trial procedures in accordance with the "patient information and informed consent" (see Appendix 1). Once signed and dated, a copy of the informed consent must be given to each patient and the original copy must be retained in the investigator's trial records. The informed consent form must be available in the case of data audits. Verification of signed informed consent and the date signed are required for enrolment into this trial.

The "Declaration of Helsinki" recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential

hazards of the trial, and discomfort it may entail, are explained to the individual by the physician. The potential patient should also be informed of her/his right to not participate or to withdraw from the trial at any time. The patient should be told that material from her/his tumour and blood and serum samples will be stored and potentially used for additional studies not described in this protocol.

If the patient is in a dependent relationship to the physician or gives consent under duress, the informed consent should be obtained by an independent physician. If the patient is legally incompetent (i.e. a minor, or mentally incompetent), informed consent must be obtained from the parent, legal guardian, or legal representative in accordance with the law of the country in which the trial is to take place. By signing this protocol, the investigator agrees to conduct the trial in accordance with GCP and the "Declaration of Helsinki".

ETOP recognises that each institution has its own local, national, and international guidelines to follow with regard to informed consent. Therefore, we provide a template information sheet and informed consent form (appendix 1), which can be edited to incorporate information specific to your institution. The template patient information sheet and informed consent has been written according to ICH guidelines which state the informed consent should adhere to GCP and to the ethical principles that have origin in the “Declaration of Helsinki”. The final version should receive the IRB / local EC approval in advance of its use. Centres should send their locally modified PIS/IC to ETOP for review and approval before submitting to their ethics committee.

20. Governance and administrative issues

20.1. Final report

A final clinical trial report will be written and distributed to health authorities as required by applicable regulatory requirements.

20.2. Steering Committee

A Steering Committee will be constituted for this trial. The Steering Committee is responsible for maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in light of emerging clinical or scientific data from other trials. Membership will include the trial chairs and co-chairs, trial statisticians, ETOP officials, representatives from participating institutions and a representative from Roche.

20.3. Independent Data Monitoring Committee

The ETOP IDMC is a standing committee of independent experts. Its role is the systematic review of the accumulating data from all ongoing ETOP sponsored trials including accrual, safety and efficacy. The primary mandate of the IDMC is to safeguard the interest and safety of the patients in the trial and to ensure the scientific integrity of the trial. Details of the particular responsibilities and procedures within the ETOP 12-17 ALERT-lung trial are summarised in the ETOP IDMC Guidelines and the trial-specific IDMC charter.

The trial will be presented for review to the ETOP IDMC at each of their bi-annual meetings. Based on this review, the IDMC recommends to the trial Steering Committee whether to continue, modify or stop the trial.

20.4. Publication

The results of the trial will be published according to the ETOP publication guidelines (appendix 2).

20.5. Clinical trial insurance

ETOP will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician. The local group/institution should report all alleged claims immediately to the ETOP coordinating office.

20.6. Quality assurance

ETOP conducts trials according to the ICH GCP guidelines. The Trial data manager reviews each eCRF as it is received. In addition, the ETOP medical reviewer reviews each case at specific time points. ETOP conducts periodic audit visits to ensure proper trial conduct, verify compliance with GCP, and perform source data verification.

The investigator should ensure that source documents are made available to appropriately qualified personnel from ETOP or its designees, or to ethics committee and health authority inspectors after appropriate notification.

At regular intervals during the clinical trial, the centre will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review trial progress, investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, dispensing IMP, compliance with protocol, drug accountability, concomitant therapy use, quality of data and storage of blood and serum samples.

20.7. Protocol adherence

Investigators ascertain that they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact ETOP or personnel monitoring the trial to request approval of a protocol deviation, as no deviations are permitted. The investigator should document and explain any deviations from the approved protocol. The investigator should promptly report any deviations to ETOP (sponsor) and to the EC concerned in accordance with the applicable EC policies and procedures. If the investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is developed and activated by ETOP (sponsor) and approved by the IRB/IEC/ERB it cannot be implemented. All protocol deviations will be recorded.

20.8. Data protection

The samples and data collected will be coded to protect patient confidentiality. Each patient will have a unique identifier assigned by the EDC facility ETOPdata. Sites are responsible to keep a patient log locally in order to be able to link the unique identifier to the record of the patient.

Biological material will be assigned the same unique identifier. No identifiable / personal data will be stored in the trial database or the tissue repositories in the central labs.

Biological material will be transferred outside the treating institution for central screening and review. Results of the assays will be coded only by the patient identifier.

Regulatory authorities and pertinent ethics committees (IRB/ERB) may have access to patient data on-site. ETOP audit or monitoring personnel will also have access to such data on-site.

20.9. Record retention

The centre must retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, patient informed consent statement, laboratory printouts, drug inventory and destruction logs, and all other information collected during the trial. These documents are to be stored until at least 15 years after the termination of the trial. ETOP guarantees access and availability of the data entered into ETOPdata for at least 15 years after the termination of the trial.

Longer retention may be required for participating centres according to national regulations.

In the event that the principal investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer has to be given to ETOP and the local ethics committee at least one month in advance.

21. References

1. Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. *Oncologist* 2013; **18**(7): 865-75.
2. Kohno T, Nakaoku T, Tsuta K, et al. Beyond ALK-RET, ROS1 and other oncogene fusions in lung cancer. *Transl Lung Cancer Res* 2015; **4**(2): 156-64.
3. Lipson D, Capelletti M, Yelensky R, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat Med* 2012; **18**(3): 382-4.
4. Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. *Nat Med* 2012; **18**(3): 378-81.
5. Takashi S, Kiyotaka Y, Miyako S, et al. A phase II open-label single-arm study of vandetanib in patients with advanced RET-rearranged non-small cell lung cancer (NSCLC): Luret study. *J Clin Oncol* 2016; **34 (suppl; abstr 9012)**.
6. Drilon A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol* 2016.
7. Drilon A, Wang L, Hasanovic A, et al. Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov* 2013; **3**(6): 630-5.
8. Gautschi O, Zander T, Keller FA, et al. A patient with lung adenocarcinoma and RET fusion treated with vandetanib. *J Thorac Oncol* 2013; **8**(5): e43-4.
9. Lee S-H, Lee J-K, Ahn M-J, et al. A phase II study of vandetanib in patients with non-small cell lung cancer harboring RET rearrangement. *J Clin Oncol* 2016; **34 (suppl; abstr 9013)**.
10. Lin JJ, Kennedy E, Sequist LV, et al. Clinical Activity of Alectinib in Advanced RET-Rearranged Non-Small Cell Lung Cancer. *J Thorac Oncol* 2016; **11**(11): 2027-32.
11. Gautschi O, Milia J, Filleron T, et al. Targeting RET in Patients With RET-Rearranged Lung Cancers: Results From the Global, Multicenter RET Registry. *J Clin Oncol* 2017; **35**(13): 1403-10.
12. Kodama T, Tsukaguchi T, Satoh Y, et al. Alectinib shows potent antitumor activity against RET-rearranged non-small cell lung cancer. *Mol Cancer Ther* 2014; **13**(12): 2910-8.
13. HOFFMANN-LA ROCHE LTD F. ALK Tyrosine Kinase Inhibitor. Alectinib Investigator Broschure Version 7; 2016.
14. Gadgeel SM, Shaw AT, Govindan R, et al. Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With ALK-Positive Non-Small-Cell Lung Cancer. *J Clin Oncol* 2016; **34**(34): 4079-85.
15. Tamura T, Kiura K, Seto T, et al. Three-Year Follow-Up of an Alectinib Phase I/II Study in ALK-Positive Non-Small-Cell Lung Cancer: AF-001JP. *J Clin Oncol* 2017; **35**(14): 1515-21.
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**(2): 228-47.