Official Title: **RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS PEMETREXED OR DOCETAXEL IN ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS PREVIOUSLY TREATED WITH PLATINUM-BASED CHEMOTHERAPY AND CRIZOTINIB**

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STATISTICAL ANALYSIS PLAN

TITLE: **RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS PEMETREXED OR DOCETAXEL IN ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON SMALL CELL LUNG CANCER PATIENTS PREVIOUSLY TREATED WITH PLATINUM-BASED CHEMOTHERAPY AND CRIZOTINIB**

PROTOCOL NUMBER: MO29750

STUDY DRUG: Alectinib (RO5424802)

VERSION NUMBER: 3.0

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SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]

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1. LIST OF CHANGES

Version	Changes
SAP Version 1	NA
SAP Version 2	• Subject eligibility updated as per Protocol Amendment • Enrollment caps removed as per Protocol Amendment • Sample size justification updated as per Protocol Amendment • Clarification that progression due to symptomatic deterioration are not considered as an event in the Progression-Free Survival as per investigator analysis. • Censoring in cases of two consecutive missing visits for tumor assessment followed by a recist documented progression is moved from the primary analysis to a sensitivity analysis. • Clarification on how the clinical cut-off is applied at the SDTM level • Addition of a time windowing for deriving visit names in the Post-Progression Treatment Period. • Clarification that the randomization date in local timezone is used in all analyses • Deletion of subgroup analyses according to prior chemotherapy and ALK rearrangement confirmed by an FDA approved test. • Definition added for the Pharmacokinetic-Evaluable population • Rephrasing of the protocol deviation section to align with the protocol deviation guide • Breslow's method specified for handling ties with Cox model in the primary efficacy endpoint section • Definition added for non-CNS progression • Replacement of Gray's test with a Stratified Fine & Gray's model for cumulative incidence functions comparison. • Pharmacokinetic analyses detailed

	• Addition of method to handle missing end date for alectinib treatment for subject that are still under treatment at the time of the cut-off. • Definition added for adverse events leading to dose reduction and drug interruption • Clarification that only PRO data collected during the FTP are analysed. • Replacement of unstructured covariance matrix with compound symmetry in mixed models for analyzing PRO repeated data, restricted to timepoints that include a minimum of 3 non-missing observation in each treatment group.
Addendum to SAP version 2	• Introduction of ITT-2, C-ITT-2, mC-ITT-2 populations including only patients randomized up to the day when the 90th randomization occurred. • Addition of Kaplan-Meier plots for NCS-progression free probability • New sensitivity analysis with an unstratified Cox model for PFS as per investigator • Addition of a table for Exposure-Adjusted Incidence Rates of adverse events • Addition of Time to Permanent Deterioration analysis in PRO outcomes • Deletion of subgroup analysis for adverse events • Repetition of boxplot figures for laboratory data after exclusion of outliers.
SAP Version 3	Updates following protocol version 6 that allows patients to cross over from chemotherapy to alectinib before progression. Details added about how to apply RPSFT method for estimating Overall Survival in presence of cross over. IRC assessment with an ad-hoc censoring date at the time when the IRC assessments were stopped.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse events
AESI	adverse events of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BID	twice daily
BOR	best overall response
C-DCR	CNS disease control rate
C-DOR	CNS duration of response
CI	confidence interval
C-ITT	patients in ITT population with CNS metastasis at baseline
CNS	central nervous system
CR	complete response
C-SAF	CNS safety population
CSR	clinical study report
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EORTC	European Organization for the Research and Treatment of Cancer
EOT	end of treatment
EQ-5D-5L	EuroQoL 5 Dimension questionnaire
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FTP	first treatment period
GGT	gamma glutamyl transferase
HR	hazard ratio
HRQoL	health-related quality of life
IC	Informed Consent
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee

Abbreviation	Definition
IHC	immunohistochemistry
INR	international normalized ratio
IRC	Independent Review Committee
ITT	Intent-to-treat
ITT- without	patients in ITT population without CNS metastasis at baseline
IxRS	interactive voice or web-based response system
KM	Kaplan Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LSMEANS	least squares mean
mC-ITT	patients in ITT population with measurable CNS metastasis at baseline
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
Pd	pharmacodynamic
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PP	per protocol
PPTP	post progression treatment period
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	preferred term
QLQ-C30	Quality of Life Questionnaire Core
QLQ-LC13	Quality of Life Questionnaire Supplemental Lung Cancer Module
QoL	quality of life
QT	Time from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RPSFT	Rank Preserving Structural Failure Time
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan

Abbreviation	Definition
SD	stable disease
SI	Système International
SOC	System Organ Class
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
TTD	time to deterioration
TTR	time to response
WBC	white blood cell

3. BACKGROUND

Lung cancer causing nearly 1.6 million death per year, is the leading cause of cancer-related mortality worldwide (GLOBOCAN 2012) and the primary form of lung cancer is non-small cell lung cancer (NSCLC), which occurs in approximately 85% of all lung cancer cases (the other forms include small cell lung cancer [10%–15%] and lung carcinoid tumor [5%]) (Molina et al. 2008).

Most of patients with advanced NSCLC show a lack of an EGFR activating mutation or ALK gene rearrangement, which occurs in approximately 85% of all cases. A standard first-line treatment for these patients is platinum-based chemotherapy (in patients with PS 0–2), although addition of bevacizumab improved outcome over platinum-based chemotherapy alone (Reck et al. 2014). Following treatment failure on first-line agents, patients with advanced NSCLC lacking EGFR/ALK alterations are then recommended to receive either pemetrexed or docetaxel as second-line therapy (Reck et al. 2014).
NSCLC patients with ALK gene rearrangements have an additional therapeutic option in the EU, where crizotinib is indicated for previously-treated ALK-positive advanced NSCLC (European Medicines Agency 2015). However, CNS progression may be particularly important for crizotinib-treated patients as the CNS is the primary site of initial treatment failure in 46%–60% of patients with ALK-positive NSCLC treated with this agent (Costa et al. 2011; Chun et al. 2012; Weickhardt et al. 2012; Costa et al. 2015; Gainor et al. 2015). Since significant morbidity is associated with CNS metastases due to the CNS involvement and to the standard forms of treatment (corticosteroids, surgery and radiation), an unmet medical need exists in this setting for therapeutic agents with better activity in the CNS.

In the EU, current options after failure of both platinum-based therapy and crizotinib, include pemetrexed and docetaxel (Reck et al. 2014), with pemetrexed being favored by a recent ESMO consensus statement (Besse et al. 2014). Nonetheless, as shown in PROFILE 1007 study (Shaw et al. 2013), the latter two agents have very poor efficacy as second-line agents (ORR, 20%; PFS, 3 months), and there is no reason to expect that the same is not true in the third-line setting. Therefore, the interest relies on finding a therapy of greater efficacy than Chemotherapy (including pemetrexed and docetaxel) in the third-line setting and in the CNS.

Several prior observations predict that alectinib, a newly developed highly-selective CNS-active ALK inhibitor with a benzo[b]carbazole scaffold, may be efficacious in both of these patient populations:

- Nonclinical data for alectinib suggest that it may be active in NSCLC even after progression on prior crizotinib therapy when the mechanism of resistance is due to acquired mutation in the ALK gene (Alectinib Investigator's Brochure for details)
- Alectinib is lipophilic and not a substrate for P-gp or the ABC transporter breast cancer resistance protein, known efflux transporters at the blood-brain barrier. Indeed, promising efficacy within the CNS has been observed with alectinib in pivotal Phase 2 studies in patients who have progressed on prior crizotinib therapy (see Section 1.3 from protocol and Alectinib Investigator's Brochure for details)
- In NSCLC patients treated with alectinib, PFS was favorable regardless of the presence or absence of CNS metastases at baseline (see Section 1.3 from protocol)

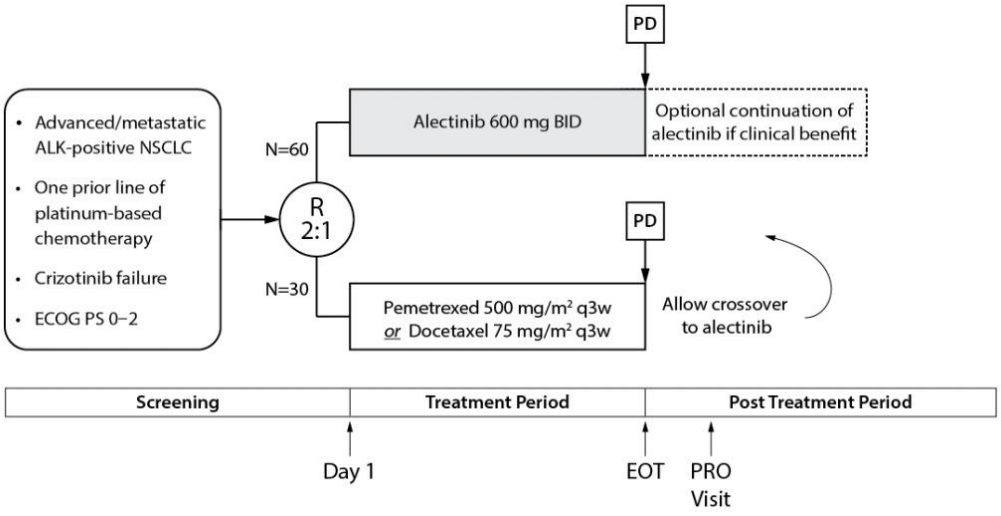
This trial is a randomized, active-controlled, multinational, multicenter Phase III open-label clinical trial of alectinib versus pemetrexed or docetaxel in anaplastic lymphoma

kinase-positive advanced non-small cell lung cancer patients previously treated with platinum-based chemotherapy and crizotinib. The purpose of this study is to determine whether alectinib, an ALK-specific TKI, provides more clinical benefit than pemetrexed or docetaxel in advanced ALK-positive NSCLC following relapse on platinum-based chemotherapy and crizotinib. The study will examine the effects of alectinib compared to chemotherapy (pemetrexed or docetaxel) in all eligible patients, as well as in the subgroup of patients with CNS metastases at baseline.
Both an independent review committee (IRC) and investigators will be responsible for assessing and reviewing tumor assessments data that will be used to determine the study endpoints. An independent data monitoring committee (IDMC) will be responsible for reviewing periodically safety data.

4. STUDY DESIGN

This trial is a randomized, active-controlled, multinational, multicenter Phase III open-label study. The study will consist of a Screening Period, a Treatment Period, a Post Progression and Post Treatment Period (**Error! Reference source not found.**). T he study will be conducted in approximately 60 centers located in approximately 15 countries worldwide.

Figure 1 Trial design



ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = End of Treatment; NSCLC = non-small cell lung cancer; PD = progressive disease; R = randomization.

Subjects eligible for this trial are patients that have:

- advanced or recurrent Stage IIIB NSCLC that is not amenable for multimodality treatment or metastatic Stage IV NSCLC received two prior systemic lines of therapy for advanced or metastatic disease, which must have included one line of platinum-based chemotherapy and one line of crizotinib (progression on or intolerability to crizotinib)
- The NSCLC must be positive for ALK as determined by ALK immunohistochemistry (IHC) or ALK fluorescence in situ hybridization (FISH). Testing must be validated and in line with published national or international guidelines

Patients will be randomized 2:1 into one of two treatment arms to receive either alectinib or chemotherapy (pemetrexed or docetaxel). Central randomization will be

performed via an interactive voice or web-based response system (IxRS) using the following stratification factors:

- Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0/1 vs. 2)
- CNS metastases at baseline (yes vs. no)
    - patients with baseline CNS metastases will be stratified by history of radiotherapy (yes vs. no)

Enrollment caps will be used to ensure that at least 50% of randomized patients will have baseline CNS metastases.

Following randomization, the experimental arm will receive oral alectinib at a dosage of 600 mg twice daily (BID), taken with food. The control arm will receive chemotherapy with either pemetrexed (500 mg per square meter of body-surface area) or docetaxel (75 mg per square meter) every 3 weeks. The first dose of the study drug (and the required premedication, when applicable) should be administered as soon as possible after randomization, preferably within 24 hours, and no later than 48 hours after randomization.

Patients on both arms will be treated with study drug (including those who cross over from chemotherapy to alectinib) until disease progression (PD), unacceptable toxicity, withdrawal of consent or death. At the discretion of the patient and the investigator, patients on the alectinib arm who show radiological progression per RECIST v1.1 will be allowed to continue receiving alectinib beyond disease progression if he or she is clinically benefitting from the drug until no further clinical benefit is to be expected, unacceptable toxicity, withdrawal of consent or death. Patients on the control (chemotherapy) arm who do not have any safety-related issues that might render the patient ineligible to receive alectinib treatment (as per safety-based inclusion criteria of the study) will be allowed to cross over to receive alectinib treatment. Patients with any safety-related issues rendering the patient ineligible to receive alectinib treatment (as per safety-based inclusion criteria of the study) will have the possibility to cross over after the safety-related issues have resolved or normalized. Upon progression on cross-over treatment with alectinib, patients will be allowed to continue receiving alectinib beyond disease progression if he or she is clinically benefitting from the drug until further disease progression, no further clinical benefit is to be expected, unacceptable toxicity, withdrawal of consent or death. Patients on either arm who opt not to continue or to cross over to alectinib will be treated at the discretion of the investigator according to local practice.
Patients will be recruited over a planned recruitment period of 12 months and then followed up to 14 months. The end of study will occur when each patient is followed up for OS up to 14 months or when 50% of randomized patients have died, whichever occurs first.

Main objectives of this study:
The primary efficacy objective for this study is to evaluate and compare the efficacy of alectinib versus chemotherapy in patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) who were previously treated with chemotherapy and crizotinib, as measured by investigator-assessed progression-free survival (PFS).

The key secondary efficacy objective for this study is to evaluate and compare between treatment groups the central nervous system (CNS) objective response rate (C-ORR) in patients with measurable CNS metastases at baseline (mC-ITT), as assessed by an Independent Review Committee (IRC).

An independent data monitoring committee (IDMC) will be responsible for reviewing periodically safety data.

4.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

4.2 OUTCOME MEASURES

4.2.1 Primary Efficacy Outcome Measures

Progression-free survival (PFS) as per investigator for all patients is defined as the time from randomization to the first documented disease progression, as determined using RECIST v1.1, or death from any cause, whichever occurs first. Progression due to a symptomatic deterioration will not be considered as an event. Patients without an event will be censored at the last tumor assessment. Patients with no baseline and/or no post-baseline assessments will be censored at the date of randomization. Patients who cross-over from chemotherapy to alectinib will be censored at the time of cross-over defined as the first day of alectinib intake following chemotherapy.

4.2.2 Secondary Efficacy Outcome Measures

4.2.2.1 Best Overall Response

The best overall response will be assessed by both IRC and investigator using the following definition.

The best overall response for a subject is defined as the most favorable outcome, according to RECIST v1.1 criteria, at any visit after randomization and after first treatment dates and up to the data cut-off or the first disease progression, whichever occurs first.

The outcomes are ordered below from most to least favorable:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Non-Evaluable (NE)

Responses of Non CR/Non PD are treated as SD.

For investigator assessments, the best overall response will be derived programmatically, according to RECIST v1.1, based on the investigator overall subject response per visit collected on the eCRF. The investigator overall subject response per timepoint will not be re-derived programmatically. Best overall response is the first occurrence of the most favorable outcome, as detailed above. A best response of CR or PR cannot be assessed unless it is confirmed, no earlier than four (4) weeks (28 days) from the time a response of CR or PR is first suspected. Please refer to the below table if the patient experienced at least one overall response of Complete Response (CR), Partial Response (PR) or Not Evaluable (NE) at any time on-treatment, the following conventions will be used to derive the confirmed best overall response:

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR a
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

If a subject experienced only CR - NE - CR, BOR will be CR.

If a subject experienced only PR - NE - PR, BOR will be PR.

If a subject experienced only PR - SD - PR, BOR will be SD.

If a subject had only one tumor assessment post baseline with an overall response of NE, then the overall response will be set to missing

A minimum interval of 5 weeks (35 days) will be considered for Stable Disease (SD) to be assigned as best overall response, i.e. in the case the single response is SD, PR or CR, this single response must have been assessed no less than 5 weeks (at least 35 days) after randomization date. A patient is assigned a BOR of PD if they have a response assessment of PD at any visit, and not a BOR of CR, PR, or SD otherwise the best overall response will be Non-Evaluable (NE).

If the subject has missing baseline tumor assessment and / or no on-treatment tumor assessment, best overall response will be Non-Evaluable (NE).

For IRC assessments, BOR will not be re-derived programmatically, this one will be provided directly by Bioclinica. The IRC BOR will correspond to the overall Best

Response taken from the Overall Assessment (Integrated Radiographic and Oncology Assessments).

The best overall response as per IRC for patients with CNS metastasis at baseline (C-BOR) will be assessed only by IRC and will be defined in a similar way by considering only lesions in the CNS.

The best overall response as per IRC for patients with measurable CNS metastasis at baseline (C-BOR) will be assessed only by IRC and will be defined in a similar way by considering only lesions in the CNS.

4.2.2.2 Progression-Free Survival

- Progression-free survival (PFS) as IRC for all patients is defined in a similar way as for PFS assessed by investigator.
- PFS as per IRC for patients with CNS metastasis at baseline will be defined in a similar way, taking into account all lesions in the body.
- PFS as per investigator for patients with CNS metastasis at baseline will be defined in a similar way, taking into account all lesions in the body.

4.2.2.3 Overall Response Rate

- Overall response rate (ORR) as per investigator for all patients is defined as the percentage of patients who attain complete response (CR) or partial response (PR), as determined using RECIST v1.1. Patients without any post-baseline assessments will be assigned to the Non-Evaluable (NE) category and regarded as non-responders. It should be noted that patients with non-measurable disease can achieve only CR and not PR.
- ORR as per IRC for all patients is defined using the same definition as for ORR as per investigator.
- ORR as per IRC for patients with CNS metastasis at baseline (C-ORR) is defined in a similar way for lesions in the CNS.
- ORR as per IRC for all patients with measurable CNS metastasis at baseline (C-ORR) is defined in a similar way for lesions in the CNS.

4.2.2.4 Disease Control Rate

- Disease control rate (DCR) as per investigator for all patients is defined as the percentage of patients with a best overall response of CR, PR or SD which lasted for a duration of at least 5 weeks.
- DCR as per IRC for all patients is defined using the same definition as DCR as per investigator.
- CNS DCR (C-DCR) as per IRC for patients with CNS metastasis at baseline is defined in a similar way for lesions in the CNS.
- C-DCR as per IRC for patients with measurable CNS metastasis at baseline is defined in a similar way for lesions in the CNS.

4.2.2.5 Duration of Response

- Duration of response (DOR) as per investigator for all patients is defined as the time from when response (CR or PR) was first documented to first documented disease progression or death, whichever occurs first. This will only be calculated for patients who have a best overall response of CR or PR. Patients who do not progress or die after they have had a response are censored at the date of their last tumor measurement.

- DOR as per IRC for all patients is defined using the same definition as DOR as per investigator.
- DOR as per IRC for patients with CNS metastasis at baseline (C-DOR) is defined in a similar way for lesions in the CNS.
- DOR as per IRC for patients with measurable CNS metastasis at baseline (C-DOR) is defined in a similar way for lesions in the CNS.

4.2.2.6 Overall Survival

Overall survival (OS) is defined as the time from randomization to death from any cause. Patients without an event will be censored at the last date known to be alive. Patients without any follow-up information will be censored at the date of randomization.
Overall survival will be analyzed for:

- all patients
- patient with CNS metastasis at baseline

4.2.2.7 Time to CNS Progression

Time to CNS progression as per IRC is defined as the time from randomization until radiographic evidence of CNS progression. Patients who died or who experience non-CNS progression will be censored at the occurrence date of the corresponding event. Patients who didn't experience any of the following events: CNS progression, non-CNS progression or death will be censored at their last tumor assessment date. CNS progression is defined as progression due to newly developed CNS lesions and/or progression of preexisting baseline CNS lesions. On the basis of RECIST v1.1, this is defined as a new post-baseline CNS/brain lesion(s) and/or an increase of ≥20% in the sum of longest diameters of the measurable baseline CNS lesions compared to nadir and/or unequivocal progression of non-measurable baseline CNS lesions. Non-CNS progression is defined as per IRC radiographic evidence of progression which is not a CNS progression.
Time to CNS progression as per IRC will be analyzed :

- in all patients regardless of their baseline status of CNS metastases.
- in patients with baseline CNS metastases
- in patients without baseline CNS metastases

4.2.3 Other Efficacy Outcome Measures

- Time to response (TTR) as per investigator for all patients is defined as the time from randomization to the first documented objective response (i.e. CR or PR). This will only be calculated for patients who have a best overall response of CR or PR.
- Time to response (TTR) as per IRC for all patients is defined using the same definition as time to response as per investigator.
- TTR for patients with CNS metastasis at baseline (C-TTR) as per IRC will be defined in a similar way for lesions in the CNS.
- TTR for patients with measurable CNS metastasis at baseline (C-TTR) as per IRC will be defined in a similar way for lesions in the CNS.

4.2.4 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Serious and non-serious adverse events
- Safety laboratory tests

- Vital signs
- ECG

4.2.5 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Sparse (pre-dose) PK samples for measurement of alectinib and its major metabolite(s) will be collected in all study patients receiving alectinib treatment

4.2.6 Patient-Reported Outcome Measures

The PRO outcome measures for this study are as follows :

- Time to deterioration (TTD) in the overall population is defined as time from randomization to the earliest time with a ≥10-point increase from baseline for symptoms domains (or decrease for functioning domains from baseline for cough, dyspnea [single item and multi-item scales]chest pain [single item], , pain in arm/shoulder and fatigue as measured by the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13)
- Time to deterioration (TTD) for a composite of three symptoms (cough, dyspnea, chest pain) in the overall population is defined as time from randomization to the earliest time with a ≥10-point increase from baseline for any component of the composite of the three following symptoms [cough, dyspnea [multi-item subscales QLQ-LC13] and chest pain]) as measured by the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13
- TTD in patients with CNS metastases at baseline
- The EORTC QLQ-C30 and EORTC QLQ-LC13 scores for the overall patient population,
- The EORTC QLQ-C30 and EORTC QLQ-LC13 scores in patients with CNS metastases at baseline.
- The EuroQoL 5 Dimension (EQ-5D-5L) questionnaire score for the overall patient population,
- The EuroQoL 5 Dimension (EQ-5D-5L) questionnaire score for patients with CNS metastases at baseline.

4.2.7 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows (additional exploratory parameters may be assessed as deemed appropriate):

- Scores from three specific questions extracted from the EORTC QLQ-BN20 questionnaire, a QoL instrument specific to brain neoplasms. The three questions are as follows: "Do you have headaches?"; "Do you have problems with coordination/balance?"; and "Did you have trouble communicating your thoughts?". Each of the three questions will be scored on a 4-point scale (1, Not at all; 2, A little; 3, Quite a bit; 4, Very much), which will subsequently be linearly transformed to a 0–100-point scale
- Corticosteroids administration in case of CNS metastasis
- Biomarkers relevant in NSCLC biology and alectinib mechanism of action (including but not limited to ALK genetic alterations)
- ALK inhibitors

- Biomarker or diagnostic assays to detect ALK mutations/fusions in plasma/tumor.

4.3 DETERMINATION OF SAMPLE SIZE

The sample size estimation was performed using EAST Software Version 6.0 based on the following statistical hypotheses:

- H0: the distribution of the PFS time is the same in the two treatment groups
- H1: the distribution of the PFS time is different in the two treatment groups
- If the hazard ratio (HR) of the investigational arm compared with the control arm with respect to PFS is assumed to be constant over time (λ), then the null (H0) and alternative hypotheses (H1) are: H0: λ=1 vs. H1: λ≠1
- Two-sided test with an alpha of 5%.

The summary of sample size calculation is provided in Table 1.

Table 1: Summary of Determination of Sample Size[a]

Primary endpoint	**Median Time to PFS (Chemo vs. Alectinib) months/HR**	**Number of Patients/Events**	**Number of Patients Per Treatment arm (Chemo vs Alectinib)**
PFS	3 vs. 7/0.43	90/50	30 vs. 60
Key Secondary endpoint	**Response (Chemo vs. Alectinib)**	**Number of Patients**	
C-ORR [b]	15% vs. 55%	24	8 vs. 16

a. 80% power, two sided alpha test at 0.05; 2:1 randomization.

b. Patients with measurable CNS metastases at baseline. 70% power, one sided alpha test at 0.05

A sample size of 90 patients (60 patients in the experimental arm [alectinib] and 30 patients in the control arm [chemotherapy]) with 50 PFS events will provide 80% power to detect a significant improvement in the median time of the primary endpoint from 3 to 7 months (i.e., HR of 0.43), based on a two sided log-rank test at an alpha level of 0.05. In the pivotal Profile 1007 trial (Shaw et al. 2013), median PFS in the chemotherapy arm among 174 patients previously treated with one platinum-based chemotherapy regimen and treated in second line with either pemetrexed or docetaxel was 3 months (95% CI, 2.6–4.3). Hence, a median PFS of 3 months for the chemotherapy arm (control arm) has been assumed.

The objective response (Shaw et al. 2013) was reported in the chemotherapy group as 20%, 95% CI (14%, 26%). at least 25% of patients with measurable CNS metastases at baseline are expected to be randomized. Approximately 24 patients with measurable CNS metastases at baseline (8 patients in control and 16 patients in experimental arm) will provide power of 70% (one sided 5% alpha test) to detect clinically meaningful difference in C-ORR of 25%, assuming C-ORR in control arm of 15%.

If superiority for the PFS endpoints is concluded, subsequent hierarchical testing for the key secondary endpoint, C-ORR in patients with measurable CNS metastases at baseline, will be performed.

4.4 ANALYSIS TIMING

iDMC Safety analyses are scheduled for the review of the accrued safety data with the following frequency:

- Once 25 patients are randomized and followed-up for 2 months
- The second meeting will take place 3 months after the first iDMC meeting
- Then, every 6 months thereafter if no safety concerns are identified.

All data after cut-off date will be excluded from the analysis. iDMC report will be provided periodically for reviewing safety data. No efficacy interim analysis is planned. Details of outputs to be produced for iDMC report will be provided in Appendix 4.

The main analysis will be performed based on the data collected until the analysis cut-off date, defined as the time when 50 subjects experienced, per investigators' assessments, death or disease progression as monitored during the trial. All tables, listings and figures detailed in the next sections will be produced for this analysis (apart biomarker analysis, in case biomarkers data are not available at that time). The Clinical Trial Report will be written based on these results.
The analysis cut-off date will be applied at the SDTM level to remove from the analysis any of the following records:

- Any individual record for patients who have an inform consent signature date after the cut-off date
- Any protocol deviation that occurred after the cut-off date
- Any assessment or evaluation that is performed after the cut-off date
- Any adverse event, medication, procedure and treatment administration that is started after the cut-off date

In all SDTM domains (in particular for adverse events and for medications) where a start date and an end date are collected, any end date after cut-off won't be imputed (ie and AE ended after the cut-off but started before will be kept as it is).

The final analysis will be performed after the end of study, i.e. when all patients are followed for at least 14 months or when 50% of randomized patients have died, whichever occurs first. The list of tables, listings and figures that will be repeated from primary analysis for Final analysis is given in Appendix 5.

5. STUDY CONDUCT

5.1 RANDOMIZATION ISSUES

Patients will be randomly assigned in a 2:1 allocation ratio to the two treatment arms via an interactive voice or web-based response system (IxRS) combined with a block-stratified randomization procedure and over a planned recruitment period of 10 months.

Randomization will guard against systematic selection bias and should ensure the comparability of treatment groups. To assist balance in important prognostic factors, randomization will be stratified by ECOG PS (0/1 vs. 2) and CNS metastases at baseline (yes vs. no). In addition, patients with baseline CNS metastasis will be stratified by history of radiotherapy (yes vs. no).

Central randomization and drug pack number allocations will be performed and managed by an IxRS.

5.2 INDEPENDENT REVIEW FACILITY

An Independent Review committee (IRC) will be reviewing tumor assessments to determine secondary efficacy endpoints. The IRC will assess CNS progression in all patients.

5.3 DATA MONITORING

An independent data monitoring committee (iDMC) will be established to monitor the progress of the study and ensure that the safety of patients enrolled in the study is not compromised. Details of the composition, roles, responsibilities and processes of the iDMC are documented in a separate iDMC charter. The iDMC will review safety data and can make recommendations to the Sponsor to stop or amend the study on the basis of safety findings. The frequency of these reviews is provided in section 4.4. No stopping for early proof of efficacy will result from any of these regular reviews.

The list of tables and figures to be provided for both open and closed session are listed in Appendix 4.

A set, referred as “closed reports” will be presented during the iDMC closed sessions. Data from both treatment periods (see definition in section 5.2) will be presented by treatment group.

A set, referred as “open reports” will be presented during the iDMC open sessions. Data from both treatment periods will be presented in a total column only, pooling data from the two treatment arms.

All iDMC “closed session” outputs will be produced by an unblinded independent statistician not otherwise involved in the conduct of the trial.

6. STATISTICAL METHODS

6.1 GENERAL DESCRIPTIVE METHODS

For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. Percentage will be calculated by using as denominators the ‘N’ in column header and will be rounded to one decimal place, unless specified otherwise. Therefore, there may be cases where for instance the total of the percentages does not exactly equal 100%. If number of patients is ‘0’ then 0 will be reported instead of ‘0 (0.0%)’.

For continuous variables, N, mean, median, standard deviation, 25th and 75th percentile, minimum and maximum values will be presented. The number of missing is displayed between brackets next to ‘N’. Mean, standard deviation, and median will be presented with one more decimal place compared to the raw data, minimum and maximum will be presented with same number of decimal places as the raw data.

In addition, hazard ratio, odds ratio will be provided with two decimals. P-value will be provided with three decimals. If <0.001, then ‘<0.001’ will be displayed.

6.2 DEFINITION OF TREATMENT PERIODS

In this study, patients in both treatment groups will be treated with study drug (alectinib or chemotherapy) until disease progression.

At the discretion of the patient and the investigator, patients on the alectinib arm who show radiological progression per RECIST v1.1 will be allowed to continue receiving alectinib beyond disease progression if he or she is clinically benefitting from the drug. Patients on the control (chemotherapy) arm who show a documented radiological progression per RECIST v1.1 will be allowed to cross over to receive alectinib. Therefore, the study is divided into two treatment periods.
The protocol version 6 introduced the possibility to patients in the control arm to cross over and receive alectinib before a document radiological progression per RECIST 1.1.

6.2.1 First Treatment Period

First treatment period (FTP) is defined as the time from randomization until

- The day before the first treatment day of alectinib beyond progression or beyond chemotherapy for subjects that crossed over or subjects that continued alectinib beyond progression
- The last assessment date otherwise.

The first day of treatment of FTP is defined as the earliest day of non-null study drug administration during FTP (i.e. alectinib or chemotherapy).

The last day of treatment of FTP is defined as the latest day of non-null study drug administration during FTP (i.e. alectinib or chemotherapy).

Baseline assessments of the FTP are defined as the latest assessment performed within 28 days prior to the first day of treatment, unless otherwise stated. Baseline tumor assessment is the latest tumor assessment performed within 28 days of randomization date. For vital signs, ECG, laboratory examinations, ECOG PS and PRO the latest available assessment within 28 days prior to or on the first day of treatment (this latest assessment will be assumed to have been performed before drug was given) will be considered as baseline evaluation.

On-treatment evaluations during the FTP will be evaluations performed on or after the first day of treatment from the FTP and

- Until 28 days from last day of treatment from the FTP or until the day before the first treatment day of alectinib beyond progression or beyond chemotherapy, whichever comes first, for subjects that crossed over or subjects that continued alectinib beyond progression
- Until 28 days from last day of treatment from the FTP otherwise.

On-treatment laboratory, ECOG PS, vital signs and ECG will be all values collected after the first day of treatment from the FTP and

- Until 28 days from last day of treatment from the FTP or until the day before the first treatment day of alectinib beyond progression or beyond chemotherapy, whichever comes first, for subjects that crossed over or subjects that continued alectinib beyond progression
- Until 28 days from last day of treatment from the FTP otherwise.

6.2.2 Post-Progression Treatment Period

Post-progression treatment period (PPTP) is applicable only for subjects that crossed over or subjects that continued alectinib beyond progression and is defined as the first treatment day of alectinib beyond progression or beyond chemotherapy until the last assessment date.

The first day of treatment of PPTP is defined as the earliest day of non-null alectinib administration beyond progression for patients who were randomized in the alectinib arm, and as the earliest day of non-null alectinib administration for patients who were randomized in the chemotherapy arm.

The last day of treatment of PPTP is defined as:
- the latest day of non-null alectinib administration beyond progression for patients who were randomized in the alectinib arm
- the latest day of non-null alectinib administration for patients who were randomized in the chemotherapy arm.

Baseline assessments of PPTP are defined as the latest assessment performed prior to the first treatment day of alectinib in the PPTP, unless otherwise stated. For laboratory examinations, vital signs, ECOG PS and ECG, the latest assessment performed on the first day of alectinib in the PPTP will be assumed to have been performed before drug was given and, thus, will be considered as baseline evaluations.

On-treatment evaluations during PPTP will be evaluations performed on or after the first treatment day of alectinib from the PPTP until 28 days from last treatment day of alectinib from the PPTP.

On-treatment laboratory, ECOG PS, vital signs and ECG will be all values collected after the first treatment day of alectinib from the PPTP until 28 days from last treatment day of alectinib from the PPTP.

Because the schedule of assessment can differ from one subject to another in the PPTP, the visit names in PPTP will be re-derived using the following windowing approach:

- Post Progression – Week 0: last assessment before on at the first day of alectinib beyond progression or beyond chemotherapy
- Then, using the relative day from treatment start day :
- Post-Progression – Week 6: 42 +-7 days
- Post-Progression – Week 12: 84 +-7 days
- Post-Progression – Week i: i*7 +- 7 days

Any post-progression visit that will not fall into one of these pre-defined windows will be considered as unscheduled. These unscheduled visits will not be presented in outputs that describe the values by timepoint. However, the unscheduled visits will be taken into account in shift tables when a worst/best value is derived all along the analyzed period.

6.3 DATA CONVENTION

The randomization date will be considered in the local timezone in analyses and outputs.

All data will be listed (e.g. pre-treatment serious adverse events), whereas only baseline and on-treatment assessment will considered for summary tables.
The following conversion factors will be used to convert days to months or years, where applicable:
- 1 week = 7 days
- 1 month = 30.4375 days

- 1 year = 365.25 days

Age at informed consent (yrs) = (date of informed consent – date of birth) / 365.25.

To calculate **duration / time between** two dates, the following convention will be used:

[Later date] – [earlier date] + 1 day.

Durations and times between two dates will be calculated only when both start and end dates are available (imputed dates cannot be used for computation, apart for overall survival when date of death has only day as missing).

The last known date to be alive will be the latest date among all dates specified in the eCRF except the following:

- Survival Follow-up date when status is either death (in this case the date of death is specified in other form/data panel) or lost to follow-up
- Study Completion/Early Discontinuation Date when reason is either death or lost to follow-up
- A sample / record with test 'Not Done'.

Imputation of "Partial Death Date" is described in section 5.16.

6.4 COMPUTING ENVIRONMENT

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.2 or newer version), unless otherwise noted.

6.5 GRADING AND CODING OF ADVERSE EVENTS, LABORATORY PARAMETERS AND MEDICATIONS

Laboratory results, adverse events, and other symptoms will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE), version 4.0, except where CTC grades are not available.

Adverse events and relevant Medical History data fields (i.e. prior symptoms / AEs) will be coded using the most recent version of MedDRA dictionary available at the time of analysis.

Prior and concomitant anti-cancer therapy / other medications will be coded using the most up-to-date version of the in house Genentech Drug Thesaurus dictionary.

Dictionary versions used will be displayed in analysis outputs.

6.6 ADJUSTMENTS FOR COVARIATES

The analysis will be adjusted for stratification factors, incorporating them as covariates in the model used to assess the treatment effect upon the efficacy endpoints (see Section 6.11). In addition, the demographics and baseline characteristics may also be included in the model in an exploratory manner to assess the covariates effect of some efficacy endpoints as described in Section 4.2.

6.7 SUBGROUP ANALYSIS

Analysis of primary endpoint and key secondary endpoint (PFS by investigator and C-ORR) will be repeated considering the following subgroups:

- Age (< 65 years vs. ≥ 65 years),
- Sex (Male, Female),
- Race (White, Asian, Other),
- ECOG performance status (0/1, 2),
- Prior radiotherapy (Yes, No),

6.8 ANALYSIS POPULATIONS

6.8.1 All Population

Full Analysis Set (FAS) is defined as all patients who signed the informed consent.

6.8.2 Randomized Population

Intent-to-treat (ITT) Population: all patients randomized in the trial, irrespective of whether or not they received trial medication. Subjects will be allocated to the treatment arm into which they were randomized (as per IxRS). The ITT population is the primary population for the analysis of efficacy endpoints.

Intent-to-treat (C-ITT) Population with CNS metastasis: patients in ITT population with CNS metastasis at baseline (as per IRC).

Intent-to-treat (mC-ITT) Population with measurable CNS metastasis: patients in ITT population with measurable CNS metastasis at baseline (as per IRC).

Intent-to-treat (ITT- without) Population without baseline CNS metastasis: patients in ITT population without CNS metastasis at baseline (as per IRC).

Intent-to-treat for protocol version 5 (ITT-2) Population: patients in ITT population that are randomized from the first randomization to the day when the 90th randomization occurred.

Intent-to-treat for protocol version 5 (C-ITT-2) Population with CNS metastasis: patients in C-ITT population that are randomized from the first randomization to the day when the 90th randomization occurred.

Intent-to-treat for protocol version 5 (mC-ITT-2) Population with measurable CNS metastasis: patients in mC-ITT population that are randomized from the first randomization to the day when the 90th randomization occurred.

6.8.3 Per Protocol Population

Per Protocol (PP) Population: patients in ITT population who have received at least one dose of study medication and have a baseline with no major protocol violations (please refer to section 6.9.2 for the definition of major protocol deviations).

Per Protocol (mC-PP) Population with measurable CNS metastasis: patients in PP population with measurable CNS metastasis at baseline (as per IRC).

6.8.4 Pharmacokinetic-Evaluable population

The PK Evaluable Population will include all patients who received any dose of alectinib and who had at least one post-baseline PK sample available. Safety Population.

6.8.5 Safety (SAF) Population

All patients who received at least one non-null dose of any trial medications. Patients will be assigned to treatment groups based on actual study medication received in the first treatment period (as per eCRF). The SAF population is the primary population for the analysis of safety parameters.
The SAF Population for PPTP will be the SAF Population restricted to patients who entered the PPTP period.
Treatment received for the FTP is 'alectinib' if patient received at least once alectinib during FTP, 'chemotherapy' otherwise.
Treatment received for the PPTP is defined only for patients entering PPTP and is 'alectinib beyond PD' if patient received at least once alectinib during FTP, 'alectinib cross over' otherwise.

Safety (C-SAF) Population with CNS metastasis: patients in SAF population with CNS metastasis at baseline (as per IRC).

6.9 ANALYSIS OF STUDY CONDUCT

6.9.1 Patient Disposition

The overall subject disposition table will be based on the FAS population and will include the following information:

- Number of subjects who signed informed consent
- Number of subjects who met all eligibility criteria: Yes/No
- Number of randomized subjects (ITT): Yes/No
- Number of randomized subjects with CNS metastases at baseline (C-ITT): Yes/No
- Number of randomized subjects with measurable CNS metastases at baseline (mC-ITT and) ITT- without : Yes/No
- Number of treated subjects in the First Treatment Period (SAF): Yes/No
- Number of treated subjects in the First Treatment Period with CNS metastases at baseline (C-SAF) : Yes/No
- Number of patients in PP: Yes/No
- Number of patients in PP with measurable CNS metastases at baseline (mC-PP): Yes/No
- Number of treated subjects in the Post-Progression Treatment Period: Yes/No

Of note, treated subjects are those that have received at least one study drug administration during the corresponding Treatment Period. Percentage of patients treated in both treatment periods and in PP populations will be based on randomized patients.

Summary of patient discontinuation and early termination will be tabulated on ITT and will display the following information:

- Number of subjects who discontinued from Alectinib treatment in FTP and the reason
- Number of subjects who discontinued from Docetaxel treatment in FTP and the reason
- Number of subjects who discontinued from Pemetrexed treatment in FTP and the reason
- Number of subjects crossing over or continuing with alectininb: Yes/No
- Number of subjects discontinuing from alectinib post-progression treatment period with the corresponding reason
- Number of subjects who discontinued the trial with the corresponding reasons

The percentage for reason of withdrawals from one treatment (i.e. alectinib, docetaxel, pemetrexed, alectinib post-progression) will be based on number of patients who were treated with the corresponding treatment.

The number of patients in ITT population will be summarized by country and site and by treatment group.

In addition, the number of subjects will be summarized by the following stratification factors as per eCRF, by treatment group on the ITT population:

- ECOG:
  - 0/1
  - 2
- History of radiotherapy and CNS metastases at baseline:
  - Subjects with no CNS metastases at baseline
  - Subjects with CNS metastases at baseline and without prior radiotherapy
  - Subjects with CNS metastases at baseline and with prior radiotherapy.

Median follow up on treatment and study will be summarized on the ITT population and estimates with corresponding 95% confidence interval (CI) will be provided using the Kaplan-Meier approach.'
The follow-up on study is defined as time from randomization to last date known to be alive. Patients who died will be censored at their date of death.
The follow-up on treatment in FTP is defined as time from randomization to end of treatment in FTP. If the treatment in FTP is still ongoing at time of cut-off date, patient will be censored at cut-off date.
The follow-up on treatment in PPTP is defined as time from start of treatment in PPTP to end of treatment in PPTP. If the treatment in PPTP is still ongoing at time of cut-off date, patient will be censored at cut-off date.

6.9.2 Protocol Deviations

A protocol deviation refers to any instance of protocol non-compliance, at different stages of the study (before study start, during screening and study conduct, end of study). All protocol deviations noted during the trial will be described.
A protocol deviation is classified as major if it impacts:

- Subject's rights, safety or welfare
- Study efficacy and/or safety results

All identified major protocol deviations will be reviewed prior to the snapshot (or DBL) by the statistician and the sponsor. Roche will approve the list of major protocol deviations which impact the efficacy.

Patients with at least one major protocol deviation that have an impact on efficacy will be excluded from the per protocol population. These can fall into the next categories:

- Any disease/condition/treatment that interfers with study
- Not eligible for treatment with docetaxel or pemetrexed
- Patients with non-confirmed diagnosis of advanced or recurrent (or metastatic non-squamous NSCLC
- Life expectancy < 12 weeks
- ALK-positive, not determined by an FISH Abbott or UHC Ventana test
- Patient with non-measurable disease per RECIST at baseline
- Patient who didn't receive 2 prior systemic lines of therapy (plat, crizo)
- Patient who did not receive any dose of study medication
- Patient who received incorrect study treatment or dose
- Patient who Received/took prohibited concomitant medication
- Continuation of study drug when study drug should be discontinued per Protocol
- Any other major deviation regarding efficacy
    - No baseline or post baseline tumor assessment
    - Omission of tumor assessment
- Patients that missed 2 consecutive tumor assessments followed by a PD

In addition, major protocol deviations will be summarized overall and by treatment groups on ITT population and will display:

- Number of patients having at least one major protocol deviations
- Number of patients having at least one major protocol deviations that have an impact on efficacy
- Number of subjects by major protocol deviations category

6.10 ANALYSIS OF TREATMENT GROUP COMPARABILITY

6.10.1 Demographics and Baseline Disease Characteristics

The following information will be summarized by treatment groups on ITT population:

- Patient Demographics
    - Age
    - Age (categories: <18, 18-64, 65-84, >=85, missing)
    - Sex
    - Ethnicity
    - Race (if Asian, region will be specified)
    - Smoking status (Tobacco use history): Never, Current, Previous
    - Female reproductive status (for female participants only. Percentage will be based on the total number of female patients)
    - Male fertility (for male only. Percentage will be based on the total number of male patients)
    - Baseline weight (kg)
    - Baseline height (cm)
    - ECOG Performance Status at baseline (0, 1, 2, 3, 4, 5)

- Lung cancer history
    - Histology (Adenocarcinoma, Squamous cell carcinoma, ...)
    - Initial diagnosis staging (Stage 0, stage I, …)
    - Current disease stage (Stage 0, Stage I, …)
    - Local ALK testing: Yes/No

- ALK local test result (Negative, Positive, Indeterminate, Missing)
- Method used for local ALK Test
- ALK confirmatory test result (Negative, Positive, Indeterminate, Missing)
- Time from initial diagnosis to randomization date (weeks)
- Time from histological or cytological confirmation date to randomization date (weeks)

- CNS metastases at baseline
  - Number of patients with any CNS metastases at baseline (as per eCRF): Yes/No
  - Number of patients with measurable CNS metastases at baseline (as per IRC): Yes/No
  - Number of patients with any CNS metastases at baseline (as per eCRF) who had a treatment for metastasis: Yes/No
  - Type of therapy for CNS metastases: Whole brain radiation therapy, Radiosurgery, brain surgery, Other

- Lesions at baseline as per IRC and as per investigator:
  - Number of site/organs involved
  - Site/organ type involved
  - Type of lesions (target only, non-target only, target and non-target)

Patient demographics and lung cancer history will also be summarized on PP, C-ITT, mC-PP populations. CNS metastases at baseline will also be summarized on PP population.

6.10.2 Medical History

Medical history, collected on "General Medical History and Baseline Conditions" eCRF page will be summarized by treatment group on the ITT population and will include the number and percentage of patients with at least one medical history by Primary System Organ Class (SOC) (sorted in descending order of the total frequency count) and by preferred term (sorted in descending order of the total frequency count within each SOC).

A patient with more than one occurrence of the same medical history in a particular system organ class/ preferred term will be counted only once in the total of those experiencing events in that particular system organ class/preferred term.

6.10.3 Prior and Concomitant Medications

6.10.3.1 Prior Anti-Cancer Treatment/Procedure

Prior anti-cancer treatments/procedures summary on ITT population will present by treatment group the following information:

- Number of subjects with prior lung surgery: Yes, No
- Number of patient by site of prior lung cancer surgery
- Number of patients with prior radiotherapy: Yes, No
- Number of patients with prior NSCLC therapy: Yes, No
- Number of patient by line of therapy: 1st line, 2nd line.

In addition, prior anti-cancer therapies will be tabulated on ITT by Drug Thesaurus Class and generic name using the in house Genentech Drug Thesaurus dictionary. Drug Thesaurus Class will be sorted in a descending order of the total frequency

count and the generic names with the highest frequency will be displayed first within each Drug Thesaurus class, unless otherwise indicated.

6.10.3.2 Non Anti-Cancer Treatment/Procedure

Prior medication is defined as any medication with end date prior to the start of the first day of treatment of FTP. For subjects that are not treated with the study treatment, all medications will be consider as prior.

Concomitant medication for FTP

Concomitant medication is defined as any medication/therapy with

- start date
  - until 28 days from last day of treatment from the FTP or before the first day of treatment from the PPTP, whichever comes first for subjects crossing over or subjects continuing alectininb beyond progression
  - last treatment day of FTP+28 days otherwise
- end-date on or after first day of treatment from the FTP or missing (ongoing).

Concomitant medication for PPTP

Concomitant medication is defined as any medication/therapy with start date before the last day of treatment from the PPTP + 28 days and end-date on or after first day of alectinib from the PPTP or missing (ongoing).

In case a concomitant medication has an incomplete or missing start date, which consequently prevents its allocation to only one treatment period, the medication will be allocated to the both treatment periods.

Prior medications will be tabulated for ITT population by treatment group and by Drug Thesaurus Class and generic name using the in house Genentech Drug Thesaurus dictionary.

Concomitant medications for FTP will be summarized for SAF population by treatment group and by Drug Thesaurus Class and generic name using the in house Genentech Drug Thesaurus dictionary.

This table will be repeated for Concomitant medication for PPTP.

Medications summary tables will present number and percentage of patients with any medication overall and by Drug Thesaurus Class and Generic Name. At each level of summation (overall, Drug Thesaurus Class and generic name, Generic Name), patients reporting more than one medication are counted only once. Drug Thesaurus Class will be sorted in a descending order of the total frequency count and the generic names with the highest frequency will be displayed first within each Drug Thesaurus class, unless otherwise indicated.

By-patient listing will be provided for the following information.

- Prior surgery/procedures using ITT population
- Concomitant surgery/procedures for FTP and PPTP using SAF population

6.10.3.3 Corticosteroid Therapy for CNS Disease

Corticosteroid therapy for CNS disease will be tabulated on ITT for FTP and PPTP separately by Drug Thesaurus Class and generic name using the in house Genentech Drug Thesaurus dictionary. Drug Thesaurus Class will be sorted in a descending order of the total frequency count and the generic names with the highest

frequency will be displayed first within each Drug Thesaurus class, unless otherwise indicated.

Corticosteroid therapies received during FTP and PPTP are defined in similar way as concomitant medications for FTP and PPTP.

In addition, change of dose of corticosteroids since last visit (increase/unchanged/decrease) will be summarized by visit during FTP according to the intake of corticosteroids at baseline (yes/no). Of note, the information of change in dose will be based on the information reported on 'CNS metastases other than baseline visit' CRF page.

6.10.4 Subsequent Anti-Cancer Therapy

Subsequent anti-cancer therapies (as reported on the 'Subsequent therapy for NSCLC Log' CRF page) will be summarized for ITT population and will present the number and percentage of patients with any subsequent anti-cancer therapies overall and by Drug Thesaurus Class and Generic Name. At each level of summation (overall, Drug Thesaurus Class and generic name, Generic Name), patients reporting more than one therapy are counted only once. Drug Thesaurus Class will be sorted in a descending order of the total frequency count and the generic names with the highest frequency will be displayed first within each Drug Thesaurus class, unless otherwise indicated.
Subsequent anti-cancer therapy and Follow-up cancer radiotherapy data will be listed separately.

6.11 EFFICACY ANALYSIS

Efficacy analysis will be conducted on ITT population and presented by treatment arms, unless otherwise stated. In case, tumor assessments are collected during the PPTP, these ones will be listed but will not be part of the efficacy analysis as not planned to be collected as per protocol. All tests will be performed at two sided alpha of 5%, unless otherwise specified. C-ORR, the key secondary endpoint, will be tested using a hierarchical approach at one sided alpha of 5%. There will be no multiplicity adjustments for testing of other secondary endpoints.

6.11.1 Primary Efficacy Endpoint

The primary efficacy objective of this study is to evaluate and compare between treatment groups the efficacy of alectinib versus chemotherapy in patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) who were previously treated with chemotherapy and crizotinib, as measured by investigator-assessed progression-free survival (PFS).

To answer the primary objective, the following hypotheses will be tested:

- H0: the distribution of the PFS time is the same in the two treatment groups
- H1: the distribution of the PFS time is different in the two treatment groups
- If the hazard ratio (HR) of the investigational arm compared with the control arm with respect to PFS is assumed to be constant over time (λ), then the null (H0) and alternative hypotheses (H1) are: H0: $\lambda=1$ vs. H1: $\lambda\neq1$

The main efficacy analysis for PFS, assessed by investigator, will be a stratified Cox model with treatment group as covariate. The model will be stratified according to the following stratification factors:

- ECOG PS (0/1 vs. 2) as recorded on the eCRF

- CNS metastases at baseline and history of radiotherapy (yes vs. no) (3 categories) as recorded on the eCRF.

Each stratum will define a separate baseline hazard functions. The PFS hazard ratio of alectinib versus chemotherapy and corresponding two-sided 95% confidence interval will be calculated using the stratified Cox model specified above. Cox proportional hazards model will be implemented using PHREG procedure with option TIES=BRESLOW. This is an approximation to the EXACT method, which assumes that there is a true but unknown ordering for the tied event times as contrasted to option TIES=DISCRETE which assumes that the events in fact occurred at exactly the same time. In addition, the null hypothesis will be tested using a stratified log-rank test taking the randomization strata (as per eCRF) into account.
The following SAS code will be used to obtain the hazard ratio and corresponding confidence interval:

```
PROC PHREG data=dataset;
MODEL survtime*censor(1)=treat cov1..<covk>;/TIES=BRESLOW;
STRATA stratum1 stratum2;
RUN;
* survtime represents variable containing event/censor times;
*censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
* cov1 to covk represent covariates (if any);
* STRATA statement to be used for stratified model only stratum1
stratum2 represent stratification variables ;
Further options to control the output may be added.
```

The following SAS code will be used to obtain the p-value:

```
PROC LIFETEST data=dataset METHOD=KM CONFTYPE=LOGLOG;
TIME survtime*censor(1);
STRATA stratum1 stratum2/group=treat;
RUN;
* stratum1, stratum2 represent the stratum variable (to be included
for stratified analysis only);
* survtime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
Further options to control the output may be added.
```

PFS for each treatment arm will be estimated using Kaplan Meier product-method estimates. PFS will be summarized by treatment groups and will display the following information:

- Number of patients in the population (N),
- Number of patients with PFS event,
- Number of patients censored,
- Median and two-sided 95% CI computed according to Brookmeyer and Crowley method,
- 25th and 75th quantile, and the corresponding two-sided 95% CI computed according to Brookmeyer and Crowley method,
- Minimum and maximum,
- The event rates at certain time points (e.g. 3, 6, 9 and higher (every 3 months) if appropriate) with the relevant two-sided 95% CIs.

Kaplan-Meier estimates and median survival times are calculated with the PROC LIFETEST procedure in SAS. The CIs of the event rates will be calculated via log-log transformation method (default option CONFTYPE=LOGLOG in SAS) based on standard errors computed using the Greenwood's formula.

The p-value from stratified log-rank test will be displayed together with the estimated PFS hazard ratio of Alectinib versus chemotherapy and associated two-sided 95% confidence intervals (CIs) obtained from the stratified Cox model.

Kaplan Meier (KM) plot of PFS by treatment arm will be generated.

Forest plots by subgroups for baseline characteristics will be generated displaying PFS hazard ratio of Alectinib versus chemotherapy and corresponding 95% CI obtained from stratified Cox model (if appropriate).

PFS time as per investigator will be listed on ITT population.

6.11.2 Secondary Efficacy Endpoints

6.11.2.1 Key Secondary Endpoint

If superiority for the PFS endpoint is concluded, subsequent hierarchical testing for the key secondary endpoint, C-ORR of patients in mC-ITT (IRC assessment), will be performed between the two treatment groups.

The C-BOR (as per IRC) will be tabulated on mC-ITT by treatment group.

The C-ORR as per IRC will be summarized on mC-ITT by the number and proportion of responders (i.e. subjects with objective response (CR or PR) as best overall response) in each treatment group, together with two-sided 95% Clopper-Pearson CI. The difference in C-ORR among treatment groups will be estimated with associated two-sided 90% and 95% CI using the Hauck-Anderson approach. The treatment difference will be tested using a Chi-square test (test at a one sided alpha level of 5%). Logistic regression will be used to assess the influence of stratification, if sufficient number of patients in C-ITT population) in an exploratory manner. The odds ratio of Alectinib vs. Chemotherapy will be summarized with the corresponding two-sided 90% and 95% Cis and the respective p-value obtained from the Wald test.

The following SAS code will be used for the logistic regression:

```
PROC LOGISTIC DATA= dataset;
CLASS treat (ref='chemotherapy')strate1 strate2 / param=ref;
MODEL response (event='1') = treat strate1 strate2 cov1 cov2 cov3/
alpha=0.10;
RUN;
* response represents the response variable;
* treat represents the treatment group;
* strate1, strate2 represents the 2 categorical covariates related to
stratification factors as per eCRF;
* cov1 cov2 cov3 represents all the baseline covariates that will be
considered;
Further options to control the output may be added.
```

Forest plots by subgroups for baseline characteristics will be generated displaying difference of proportions of Alectinib minus chemotherapy and corresponding 95% CI.

All corresponding information, including the C-BOR as per IRC will be listed using the mC-ITT.

All analyses for the key secondary endpoint will be replicated on the ITT-2 population.

6.11.2.2 Progression Free Survival

The same analysis as those described for the primary endpoint will be repeated for the following outcomes:

- PFS as assessed by IRC on ITT population
- PFS as assessed by investigator on C-ITT
- PFS as assessed by IRC on C-ITT.
- PFS as assessed by investigator on ITT-2
- PFS as assessed by IRC on ITT-2

For PFS analyses requiring the IRC assessment (PFS as per IRC), an ad-hoc censoring will be applied at the date of 03JUL2017, which corresponds to the time when the IRC assessments were stopped for the study.
All corresponding PFS information will be listed.

6.11.2.3 Overall Survival

This study is not powered for OS, so adequately powered statistical testing for this endpoint will not be possible. However, a stratified log rank test will be provided in an exploratory manner to assess the difference between treatment arms for OS.

The same analysis as those described for the primary endpoint will be repeated for OS on ITT population and on C-ITT. The survival rate will be displayed at the following time points: 6, 9, 12 and higher (every 3 months) if appropriate.

By patients listing will be provided for OS times and corresponding information.

In order to explore the impact of cross-over on the Overall Survival difference between treatment arms, the Rank Preserving Structural Failure Time (RPSFT) methodology, originally developed by Robins and Tsiatis [2] and referred in Watkins at al. [3], will be applied in a secondary analysis. This method will estimate overall survival measured from the time of cross over by applying an estimate of the benefit of the alectinib treatment (derived iteratively and referred to as the inverse of the acceleration factor β). The total overall survival time, defined as the sum of time from randomization to cross-over and the estimated survival time after cross-over will then be analyzed using the same methodology as for the primary analysis of OS.

The first day of treatment in the Post-Progression Treatment Period will be used as the cross-over date for all patients that started the study in the chemotherapy group.
A grid estimation approach will be used to estimate the acceleration factor β. This involves assuming a range of β and for each value of β using the Acceleration Failure Time (AFT) model to derive a latent survival time for every patient. These latent survival times can then be compared using the stratified log-rank test, and the value of β that leads to this test statistic which shows no difference between treatment arms will be taken as the best estimate of β.

The SAS code for estimating the acceleration factor, re-censoring the data, and estimating an adjusted confidence interval for the hazard ratio is provided in Appendix 6.

A sensitivity analysis of overall survival adjusted with the RPSFT method will be performed by using an unstratified log-rank test and a hazard ratio computed from an unstratified proportional hazards model.

6.11.2.4 Overall Response Rate and Disease Control Rate

Same analysis as described for C-ORR but with two-sided test at 5% and 95%CI (instead of 90%CI) will be provided for the following outcomes:

- BOR (assessment by investigator and IRC) on ITT population
- ORR (assessment by investigator and IRC) on ITT population
- C-BOR (assessment by IRC) for C-ITT
- C-ORR (assessment by IRC) for C-ITT
- DCR (assessment by investigator and IRC) on ITT population
- C-DCR (assessment by IRC) for C-ITT
- C-DCR (assessment by IRC) for mC-ITT
- BOR (assessment by investigator and IRC) on ITT-2
- ORR (assessment by investigator and IRC) on ITT-2
- DCR (assessment by investigator and IRC) on ITT-2

The following information will be listed. Separate listings will be performed.

- Tumor assessment and overall response per timepoint as per investigator for ITT
- Tumor assessment and overall response per timepoint as per IRC for ITT
- Best overall response as per IRC and investigator for ITT
- Overall response per timepoint in CNS lesion as per IRC for C-ITT
- C-BOR as per IRC for C-ITT

6.11.2.5 Duration of Response

The following outcomes will be summarized by treatment groups:

- Duration of response (assessed by investigator and IRC) on ITT population restricted to patients with BOR of CR or PR
- C-DOR (assessed by IRC) (if there is a sufficient number of CNS response)
    - On C-ITT restricted to patients with C-BOR of CR or PR
    - On mC-ITT restricted to patients with C-BOR of CR or PR

Summary table for duration of response will display, by treatment group, the number of patients with best overall response CR or PR (N), number of patients with progression or death, number of patients censored, min, max, 25th quantile, 75th quantile and median with the associated two-sided 95% CIs computed according to Brookmeyer and Crowley method. The p-value from stratified log-rank test will be displayed together with the estimated hazard ratio of alectinib versus chemotherapy and associated 95% confidence intervals (CIs) obtained from the stratified Cox model.

The duration of response as per IRC assessment will be censored at the date of 03JUL2017, which corresponds to the time when the IRC assessments were stopped for the study.

Duration of response as per IRC and investigator will be listed separately.

6.11.2.6 Time to CNS Progression

Time to CNS progression analyses will be provided using all patients regardless of their baseline status of CNS metastases. Time to CNS progression analyses will also be provided on the subgroups of patients with CNS metastases at baseline and patients without CNS metastases at baseline.
Time to CNS progression analysis will be performed on ITT, ITT-2, C-ITT and ITT-without as applicable.

Summary table for time to CNS progression as per IRC assessment will display, by treatment group, the number of patients in the population (N), number of patients with CNS progression, number of patients censored, min, max, 25th quantile, 75th quantile and median with the associated two-sided 95% CIs computed according to Brookmeyer and Crowley method.

Analysis of time to CNS progression will be performed using competing risk analysis for patients experiencing a CNS progression. The competing events are death and non-CNS progression. A non-CNS progression will be defined as the first progression (as per IRC) for subjects that don't have a CNS progression, or as the first progression that occurs before the first CNS progression (if any).

A stratified Cox model with treatment group as covariates will be performed on the cause specific hazard function for CNS progression. Patients with non-CNS progression or death will be censored at the time of the event. The estimated HRs and the associated two-sided 95% CI will be displayed. Treatment groups will be compared by means of a stratified two-sided log-rank test applied on the cause specific hazard function of CNS progression.

As supportive analysis, the time to CNS progression will be analyzed on the basis of cumulative incidence function. The probability of having a CNS progression and a non-CNS progression will be estimated using a cumulative incidence function for the specific event (CNS progression and Non-CNS progression).
Death and non-CNS progression will be considered as competing events for the CNS progression cumulative incidence. Death and CNS progression will be used as competing events for the non-CNS cumulative incidence.
The cumulative incidence functions will be estimated by using the SAS macro %cumincid. A stratified Fine & Gray's model will be applied on cumulative incidence function to test the difference among treatment groups. The Fine & Gray model will be fit by the use of a weighted proportional hazard model, with the treatment group entered as the unique covariate and the stratification factors (from eCRF) used to stratify the hazard baseline function. The individual weights will be calculated with the published sas macro %PSHREG.

The following SAS code will be used to estimate the cumulative incidence functions:

```
%CUMINCID(DATA=dataset,TIME=survtime,STATUS=Status,EVENT=1,COMPETE=2,CEN
SORED=0,STRATA=Treat, OUT=outds);
The parameters for the %CIF macro from SAS are as follows:
_ DATA=dataset specifies the data set to analyze.
_ TIME=Survtime specifies the time variable.
_ STATUS=Status specifies the name of the numeric variable whose values
indicate whether an observation corresponds to the event of interest,
the competing events, or is censored: 0 for censoring, 1 for event of
interest (CNS progression), or 2 for competing risk (non-CNS
progression, death)
_ EVENT=1 specifies the value for the event of interest.
_COMPETE=0 specifies the value for the competing event
_ CENSORED=0 specifies the value used to indicate censoring. Values that
are specified with the STATUS=parameter rather than those specified with
the EVENT= and CENSORED= parameters are for competing risks.
_ STRATA=Treat requests a cumulative incidence curve for each treatment
group
_OUT= outds specifies the name of the output dataset
```

The following SAS code will be used to fit the Fine & Gray model:
First, the individual weights will be calculated with the %PSHREG macro

```
%PSHREG(DATA=dataset,ID=id,TIME=survtime,CENS=STATUS,VARLIST=Treat,OUT=o
utds_wgt)
```

```
Where
_DATA=dataset specifies the data set to analyze
_ID=id specifies the subject unique identifier
_TIME=survtime specifies the time variable
_CENS=STATUS specifies the name of the numeric variable whose values
indicate whether an observation corresponds to the event of interest,
the competing events, or is censored
_VARLIST= Treat specifies the list of covariates to include in the
model, here only the treatment variable
OUT=outds_wgt specifies the name of the output dataset
```

Second, a weigthed PHREG procedure will be used to fit the Fine & Gray model:

```
%PHREG DATA= outds_wgt COVS(AGGREGATE) ;
MODEL (_start_,_stop_)*_censcrr_(0) = Treat / RL=PL;
WEIGHT _weight_;
ID id;
STRATA strate1 strate2;
ODS OUTPUT ParameterEStimates = PE;
RUN;
```

The summary table will include the number of subjects at risk, estimates of the cumulative incidence rate (%) for both treatment groups and two-sided 95% CIs. The standard error of cumulative incidence will be computed using the counting process method. The p-value coming from the Wald's test associated to the treatment variable in the Fine & Gray's model will also be displayed.

Plots of the estimated cumulative incidence rate will be displayed by treatment group. Plots of Kaplan-Meier estimates for CNS-progression free probability will be displayed by treatment group on ITT, C-ITT and ITT-without populations.

All the corresponding information related to time to CNS progression as per IRC will be listed.

6.11.2.7 Other Efficacy Endpoint

A summary (number and percentage) will be provided by treatment arms on ITT and on C-ITT, for the following information:

- Number of patients who has a documented PD (assessment by investigator and IRC) in the FTP
- Number of patients who agree to continue or cross-over to receive alectinib beyond progression based on the treatment Completion/Early Discontinuation CRF form. (Percentage is based on patients who have a documented PD in the FTP).

The following outcomes will be summarized by treatment groups using descriptive statistics:

- Time to response (TTR) (assessed by investigator and IRC) on ITT population restricted to patients with BOR of CR or PR ;
- C-TTR (assessed by IRC)
  - on C-ITT restricted to patients with C-BOR of CR or PR
  - on mC-ITT restricted to patients with C-BOR of CR or PR

By-patients listings will be provided for

- TTR as per IRC and investigator
- C-TTR as per IRC.

6.11.3 Exploratory Efficacy Endpoints

Not applicable.

6.11.4 Sensitivity Analyses

The following sensitivity analyses will be provided on primary efficacy endpoint (PFS per investigator):

- An unstratified analysis using an unstratified Cox model and an unstratified Log-rank test.
- The same analysis as the primary analysis but using different censoring rules:
    - In case patients received subsequent therapies before PD, they will be censored at their last tumor assessment prior the first day of treatment with the subsequent therapy. Of note, subsequent therapies only include therapies as reported on the 'Subsequent Therapy for NSCLS Log' CRF page.
    - For patients who have documented PD or Death occurs after ≥ 2 missed tumor assessments (defined as a time from the last previous tumor assessment to the event higher than 12+1 weeks). These patients will be censored at the last tumor assessment prior to the missed assessments.

Analysis on primary and key secondary efficacy endpoints will be repeated on PP population and mC-PP population respectively. If the PP population includes at least 90% of subjects in the ITT population, additional efficacy analyses on the PP population will be omitted as the differences in the results based upon these two populations are expected to be negligible.

6.12 PHARMACOKINETIC ANALYSES

Pharmacokinetic analysis will be handled by the Clinical Pharmacology department at Roche.

PK Pre-Dose (C trough) concentrations of alectinib and M4 at each nominal point will be presented in listings and descriptive summary statistics including means, standard deviation (SD), minimum, median, maximum, coefficient of variation (CV), geometric means and CV of geometric mean.

6.13 SAFETY ANALYSES

Safety summaries will be produced on data collected during FTP for the SAF and the C-SAF by treatment group (i.e. alectinib and chemotherapy), unless otherwise specified. Safety summaries will be repeated on data collected during PPTP for SAF population, if the corresponding data are collected. Safety summaries will be repeated on data collected during PPTP for C-SAF population, if data are collected for at least 10 patients per treatment group, otherwise, data will be listed only.

No inferential statistical analyses are planned.

6.13.1 Exposure of Study Medication

6.13.1.1 Treatment duration and dose exposure

Definition of treatment duration, cycle initiated and dose exposure variables are in Table 2.

Table 2: Exposure Definitions

	Alectinib	Docetaxel	Pemetrexed
Time on Treatment for FTP (in weeks)	(last alectinib treatment day from FTP - first alectinib treatment day from FTP +1)/7	[min (last treatment day of Docetaxel/Pemetrexed +20, death date, discontinuation date of Docetaxel/Pemetrexed)) – (first treatment day of Docetaxel/Pemetrexed) +1] / 7. Note: Subjects still on treatment will be censored at minimum date between (cut-off date, last known drug administration date)	
Time on treatment for PPTP (weeks)	(last day of alectinib from PPTP - first day of alectinib from PPTP +1)/7	Not applicable	
Number of cycle initiated applicable for FTP only	Not applicable	The number of cycle initiated will correspond to the number of (non-null) treatment doses administered in FTP as only one dose have to be administered per cycle.	
Cumulative dose in FTP	a) If “BID” is ticked as frequency on study drug administration eCRF page: sum of all dose administered per recordin FTP where a dose per record corresponds to: dose administered * 2 * (stop date administered - start date administered +1) b) If “QD” is ticked as frequency on study drug administration eCRF page: sum of all dose administered per record in FTP where a dose per record corresponds to: dose administered * (stop date administered - start date administered +1) unit: mg	sum of all dose administered in FTP as collected on the study drug administration CRF page unit: mg/m^2	

	Alectinib	Docetaxel	Pemetrexed
Cumulative dose in PPTP	same definition as FTP but considering only data from the PPTP unit: mg	Not applicable	
Dose intensity in FTP	Cumulative dose from FTP / (time on treatment from FTP *7) Unit: mg/day	Cumulative dose in FTP / number of cycles initiated Unit: mg/m2 q3w or mg/m2 q6w	
Dose intensity in PPTP	Cumulative dose in PPTP / (time on treatment in PPTP *7) Unit: mg/day	Not applicable	
Planned dose in FTP	2*600=1 200 mg / day	75 mg/m2 q3w if every 3 weeks	500mg/m2 q3w if every 3 weeks
Planned dose in PPTP	2*600=1 200 mg / day	Not applicable	
Relative dose intensity in FTP (RDI) (%)	100 * (dose intensity in FTP) / (planned dose in FTP)		
Relative dose intensity in PPTP (RDI) (%)	100 * (dose intensity in PPTP) / (planned dose in PPTP)	Not applicable	

In case a subject is still under treatment at the time of cut-off, and the last record for the alectinib administration contains a start date but not an end date, the end date of alectinib administration will be imputed with the cut-off date.
In addition, the cut-off date will replace the end of alectinib administration in case there is an end date after the cut-off date.

Time on treatment for FTP and for PPTP will be summarized by treatment groups using descriptive statistics.

In addition, number of cycles initiated by patients considered as both continuous and categorical variables will also be summarized by treatment groups using descriptive statistics.

The following information will be tabulated by study drugs received during FTP (i.e. alectinib, docetaxel, pemetrexed) using descriptive statistics:

- Summary of drug exposure

- Cumulative dose
- Dose intensity
- Relative dose intensity.

This summary will be repeated for alectinib during the PPTP.

6.13.1.2 Dose Interruption or Cycle Delayed

Cycle delay

Cycle delay is applicable to the following treatments: pemetrexed and docetaxel.
A cycle delay for a treatment will be defined as the number of days in excess of the expected days between two consecutive doses of the corresponding treatment (21 days as the drug is administered every 3 weeks). An excess of more than 3 days will qualify the cycle as delayed. For any cycle delay identified, the reason for cycle delayed will be recovered from the study drug administration eCRF pages (reason for modification). A category “unknown” will be used in the event that there is no reason reported for a cycle delayed.

Dose interruption

Dose interruption is applicable to alectinib in FTP and in PPTP. Alectinib is considered as omitted on a particular day if it was not administered on that day. Alectinib will be considered as interrupted if it is omitted for two or more consecutive days.

Dose interruption/cycle delayed will be summarized by treatment groups for FTP. The following will be displayed:

- Number of patients with at least one dose interruption/cycle delayed
- Dose interruptions/cycles delayed per patient: as continuous and as categorical (1, 2, 3, or ≥3).

Dose interruption summary table will be repeated for alectininb during the PPTP.

6.13.1.3 Dose Reduction

Dose reduction is applicable to alectinib administration in both FTP and PPTP.

Alectinib starting dose is 600 mg twice daily. The protocol allows for a maximum dose reduction to 300 mg twice daily (see Table 3).

Table 3: Dose reduction Schedule

Dose reduction schedule	Dose level
Starting Dose	600 mg twice daily
First dose reduction	450 mg twice daily
Second dose reduction	300 mg twice daily

Dose reduction will be derived programmatically using actual dose received and dose reduction schedule (see Table 3). For case where a dose reduction is derived as per Table 3 but the reason is not collected in eCRF, then the reason will be set as missing.

Dose reduction will be tabulated only for alectinib treatment group in FTP and will present:

- Number of patients with at least one dose reduction
- Number of dose reductions per patient: 1 dose reduction, 2 dose reductions
- Reason for first dose reduction

- Reason for second dose reduction.

This table will be repeated for patients receiving alectinib in PPTP.

By patients listings will be provided for the following information.

- Drug administration.
- Drug exposure,
- Dose interruption/cycle delayed,
- Dose reduction and reason.

6.13.2 Adverse Events

Adverse events variables are defined in Table 4.

Table 4 : Adverse events definitions

Variable	Definition
Treatment Emergent Adverse Events (TEAEs)[1] for FTP	Any adverse events (serious and non-serious) with an onset date on (only if the "Event occurred prior to first study drug administration" from the AE eCRF page is not checked) or after the first day of treatment from FTP and until : • last day of alectinib administration from the FTP +28 days or the day before the first day of alectinib administration from the PPTP, whichever comes first, for subjects crossing over or continuing with alectinib after progression • last day of alectinib administration from the FTP +28 days otherwise
Treatment Emergent Adverse Events (TEAEs)[1] for PPTP	Any adverse events (serious and non-serious) with an onset date on or after start date of the first day of alectinib administration from the PPTP and up to 28 days from the last day of alectinib administration from the PPTP
Selected adverse events ,	Selected AEs related to ALK inhibitors and alectinib data are categories of AEs from different SOC (System Organ Class) put into one same 'basket) given one medical criteria relevant for the drug/disease area. The categories are defined by Roche safety and implemented by statistical programming .
Adverse Events NCI CTCAE grade	The adverse events grade displayed in the AE summary table will be the one with tick box checked for "AE most extreme NCI CTCAE grade". Any AEs with a missing CTC grade will be reported in the "missing" category grade.
Serious Adverse Events (SAEs)	Any adverse events with "Serious" box checked for "Is this AE non-serious or serious?". In case of missing seriousness, TEAE will be considered serious.

Variable	Definition
Adverse events related to <Alectinib, Pemetrexed, Docetaxel >	Any adverse events with 'Yes' for "AE suspected to be caused by < Alectinib, Pemetrexed, Docetaxel >"
Adverse Events with fatal outcome	Any adverse events with tick box checked for "It resulted in death"
Adverse events leading to <Alectinib, Pemetrexed, Docetaxel > discontinuation	Any adverse events with an "Action taken with < Alectinib, Pemetrexed, Docetaxel > due to SAE/AE" of "drug withdrawn"
Adverse events leading to <Alectinib, Pemetrexed, Docetaxel > dose reduction	Any adverse events with an "Action taken with < Alectinib, Pemetrexed, Docetaxel > due to SAE/AE" of "Dose reduced"
Adverse events leading to <Alectinib, Pemetrexed, Docetaxel > drug interruption	Any adverse events with an "Action taken with < Alectinib, Pemetrexed, Docetaxel > due to SAE/AE" of "Drug interrupted"
Adverse events of Special Interest (AESI) based on eCRF categories	Any adverse events with "Yes" box checked for "Is this an adverse event of special interest?" in the eCRF AESIs will be summarized based on the tick box from the eCRF. The categories from the AE eCRF page will be considered.

(1) Of note, in case an event has an incomplete or missing start date, which consequently prevents its allocation to only one treatment period of the trial, the event will be allocated to both treatment periods.

An overview table will be provided by treatment, and will display number and percentage of patients with at least one:

- TEAE
- TEAE by CTC grade: 1, 2, 3, 4, 5, >=3,missing
- TEAE related to study drug
- Serious TEAE related to any study drug
- TEAE of special interest
- Selected TEAEs
- Serious TEAE
- Serious TEAE of special interest
- TEAEs leading to treatment discontinuation of any study drug
- TEAE with fatal outcome

The incidence of TEAEs will be summarized by worst intensity (grade 1 - grade 5, missing, overall) and by treatment groups and will display number of patients with at least one TEAE, for the following AEs

- TEAE
- TEAE related to any study drug
- Selected TEAEs leading to discontinuation of any study drug

The TEAE tables will include the number and percentage of patients with at least one AE, by MedDRA primary System Organ Classes (SOC) (sorted in descending order of the total frequency count) and MedDRA Preferred Terms (PT) (sorted in descending order of the total frequency count within each SOC in the 'alectinib' column) unless otherwise indicated. A patient with more than one occurrence of the same adverse event in a particular system organ class/preferred term will be counted only once in the total of those experiencing adverse events in that particular system organ class/preferred term.

The selected TEAEs table will include the number and percentage of patients with at least one AE, by Grouped term (set of AE preferred term selected by Roche Safety department) (sorted in descending order of the total frequency count in the 'alectinib' column) and MedDRA Preferred Terms (PT) (sorted in descending order of the total frequency count within each Grouped term in the 'alectinib' column) unless otherwise indicated. A patient with more than one occurrence of the same adverse event in a particular grouped term/preferred term will be counted only once in the total of those experiencing adverse events in that particular Grouped term/preferred term.

The above summary tables will be repeated for the following categories of TEAEs; however the following tables will not be split by intensity.

- TEAE with NCI CTCAE grade >=3
- TEAE of special interest based on the eCRF categories
- Serious TEAE related to any study drug
- Serious TEAE
- Serious TEAE of special interest
- TEAE with fatal outcome

All the above tables will be generated on the Safety population for the FTP and the PPTP. These tables will be repeated on C-SAF.

Time to first occurrence of selected TEAEs in weeks is defined as the time from the first treatment day to the first occurrence date of a selected TEAEs. Subjects with no event will be censored at the minimum date between (last treatment administration + 28 days, death date).

Time to first occurrence of selected TEAEs will be summarized by treatment groups for the FTP and for the PPTP on the Safety population and will display the following information:

- Number of patients in the population (N),
- Number of patients with the event of interest,
- Number of patients censored,
- Median and two-sided 95% CI computed according to Brookmeyer and Crowley method,
- 25th and 75th quantile, and the corresponding two-sided 95% CI computed according to Brookmeyer and Crowley method,
- Minimum and maximum.

Kaplan-Meier estimates and median survival times are calculated with the PROC LIFETEST procedure in SAS.

Kaplan Meier plot will be generated to display the cumulative incidence on the vertical axis when time to first selected TEAEs for the FTP is estimated on the Safety population.

In addition, by-patients listing will be provided. The following items will be listed.

- All adverse events
- All AESI based on the eCRF categories
- All selected TEAEs
- All serious adverse events
- All adverse events leading to treatment discontinuation

Of note, TEAEs will be flagged for each treatment period as well as patients with CNS metastases at baseline.

In addition to the outputs presenting the frequencies of adverse events, the Exposure-Adjusted Incidence Rates (AEIR) of adverse events will be presented in patient-month unit on the SAF population for the first treatment period (FTP) using the following definition:
Let t_i denote the time to the first event for subject i, and l_i denote the exposure time for emergent adverse events (ie time from the first day of treatment in FTP to the last day of treatment in FTP + 28 days or to the day before the first treatment day in PPTP) expressed in months for subject i in FTP, then the exposure adjusted incidence rate is defined as:

$$\text{EAIR} = \frac{\sum_i I(t_i \le l_i)}{\sum_i \left[t_i I(t_i \le l_i) + l_i \{1 - I(t_i \le l_i)\} \right]}$$

6.13.3 Death

A summary table will be provided by treatment groups on SAF for the FTP and will present:

- Number of patients who died with the corresponding cause of death
- Number of patients who died within 28 days from last day and the corresponding cause of death.

This table will be repeated on C-SAF and will also be generated for PPTP.

Listing of deaths, dates and cause of deaths will be provided; patients with CNS metastases at baseline will be flagged.

6.13.4 Vital Signs

Vital sign parameters include:

- Temperature
- Pulse
- Respiratory rate
- Systolic blood pressure

- Diastolic blood pressure
- Weight(kg)
- Height(cm)
- Body surface area
- Oxygen saturation

Actual value and change from baseline for pulse rate and systolic and diastolic blood pressure will be summarized for FTP by treatment groups, for each visit using descriptive statistics. These summary tables will be repeated for alectinib during the PPTP.

All vital signs data will be listed.

6.13.5 Laboratory Data

Laboratory parameters include:

- Hematology: white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, platelet count, neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells
- Biochemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatine, total protein, eGFR, albumin, phosphorus, calcium, total bilirubin, direct bilirubin, alkaline phosphatase, ALT, AST, gamma-glutamyl transferase (GGT)
- Urinalysis: pH, gravity, glucose, protein, ketones, blood

Summary tables and figures will be provided for selected parameters only:

- Hematology values: hemoglobin, neutrophils, platelets
- Liver values: ALT, AST, ALP, total and direct bilirubin
- Renal values: creatinine, eGFR
- Creatinine phosphokinase (CPK)

Clinical laboratory values will be expressed using conventional SI units.

When applicable, laboratory tables will display their High (hyper)/Low (hypo) values of a specific parameter (e.g. calcium (high) and calcium (low) in separate tables.

In case of missing normal ranges for parameters that are not differential and have only grade 1 defined from normal ranges (e.g. Neutrophils, WBC, Albumin…) the worst case scenario will be apply i.e. grade 1.

A “Missing” category will be reported for subjects with missing grades or missing reference range indicators at baseline and/or on-treatment and subjects with no laboratory assessments.

The selected laboratory parameters will be tabulated for both FTP and PPTP separately using the shift from baseline in the CTC grade. The summary of the baseline grade will be summarized versus the worst CTC grade with the worst grade per subject defined as the highest CTC grade among on-treatment evaluations. If there is no on-treatment evaluation then the worst grade will be set to ‘Missing’. This applies to hematology and chemistry parameters which can be graded as per NCI CTCAE version 4.0.

Shift table from baseline to worst on-treatment value for hematology and chemistry parameters which cannot be graded as per NCI CTCAE will be produced for the FTP and PPTP separately with the following categories:

- Baseline: Low/Normal/High/Missing/Overall
- Worst on-treatment: Low/Normal/High/Missing/Overall

Patient with High and Low for the same laboratory test (at different visits) is counted for each direction in summary tables.

Boxplot will be provided overtime and by treatment group on actual values of selected hematology and chemistry laboratory parameters. The X-axis will display the time (in weeks). Plots will be performed for FTP and PPTP separately.

The boxplot figures will be replicated after the exclusion of outliers. The outliers will be defined as any result that is greater than Q3+1.5*IQR or lower than Q-1.5*IQR, with IQR denoting the interquartile range from the observations for a given parameter/period/treatment group/visit.

All laboratory values will be listed. Separate listings will be generated to include all abnormal laboratory values.

6.13.6 Electrocardiogram

The following information will be provided for the FTP and PPTP.

- A shift table (baseline vs. worst on-treatment value) for Qualitative ECG results over time presenting the number of patients by categories: Normal/Abnormal, not clinically significant/Abnormal, clinically significant/unable to Evaluate/Missing
- Summary of QTcF (in categories) over time presenting the number of patients with QTcF in categories: <=450 ms/ >450 ms - <=480 ms/>480 ms - <= 500 ms / >500 ms
- A listing of patients with at least one abnormality and or with a QT prolongation (i.e. QTcF > 450 ms) presenting all data collected through the ECG eCRF form will be provided.

In addition, all ECG data will be listed.

6.14 PATIENT-REPORTED OUTCOME ANALYSES

Analysis of PRO outcomes will be done on ITT population using data collected during the FTP, excluding from the analysis the post-treatment visits which will be reported only in the listing.

6.14.1 Definition and Scoring Rules

6.14.1.1 EORTC QLQ-C30

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items (see Table 5) - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents

a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

Scoring of QLQ-C30

For each scale, the RawScore, RS, is the mean of the component items:

$$\text{RawScore} = RS = (I_1 + I_2 + \ldots + I_n)/ n,$$

where I_1, I_2 … In are the answers to the items contributed to a scale.

Then, a linear transformation is used to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms

- For Functional scales:
  Score = {1- (RS -1)/ range} * 100
- For Symptom scales / items and Global health status / QoL:
  Score = {(RS -1)/ range} * 100.

Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with range = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have range = 1.

An example is provided below for computation of Emotional functioning and Fatigue scores.

- Emotional functioning score is given by
  RawScore = (Q21 + Q22 + Q23 + Q24)/4
  EF score = {1 - (RawScore - 1)/3} * 100
- Fatigue score is given by
  RawScore = (Q10 + Q12 + Q18)/3

If at least half of the items from the scale been answered, then the score will be calculated using the non-missing answered, the score will be set as missing otherwise. For single-item measures, the score will be set to missing.

Table 5: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

6.14.1.2 EORTC QLQ-LC13

The lung cancer module (EORTC QLQ-LC13) is meant for use among a wide range of lung cancer patients varying in disease stage and treatment modality (Bergman et al., 1994). The module comprises 13 questions and is designed for use among patients receiving treatment with chemotherapy and / or radiotherapy. The QLQ-LC13 includes questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea and site specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication.

Scoring of QLQ-LC13

The lung cancer module incorporates one multi-item scale to assess dyspnea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales / single items of the QLQ-C30. Details of multi-item scales information are in Table 6.

A score for a specific scale will be calculated only if all items of the scale are non-missing; otherwise, it will be set as missing.

Table 6: Scoring the QLQ-LC13

Scale name	Scale	Number of items	Item range*	QLQ-LC13 Item numbers
Dyspnoea	LCDY	3	3	33,34,35
Coughing	LCCO	1	3	31
Haemoptysis	LCHA	1	3	32
Sore mouth	LCSM	1	3	36

Dysphagia	LCDS	1	3	37
Peripheral neuropathy	LCPN	1	3	38
Alopecia	LCHR	1	3	39
Pain in chest	LCPC	1	3	40
Pain in arm or shoulder	LCPA	1	3	41
Pain in other parts	LCPO	1	3	42
Dyspnoea at Resting	LCDYR	1	3	33
Dyspnoea at Walking	LCDYW	1	3	34
Dyspnoea at Climbing Stairs	LCDYC	1	3	35

* "Item range" is the difference between the possible maximum and the minimum response to individual items.

6.14.1.3 EORTC QLQ-BN20

The brain cancer module (EORTC QLQ-BN20) is intended for patients undergoing chemotherapy or radiotherapy. It includes 20 items assessing future uncertainty, visual disorder, motor dysfunction, communication deficit and other disease symptoms (e.g. headaches and seizures) and treatment toxicities (e.g. hair loss) (Osoba et al., 1996).

Patients will complete only three specific questions extracted from the EORTC QLQ-BN20 questionnaire. The three questions are as follows:

- Do you have headaches?
- Do you have problems with coordination/balance?
- Did you have trouble communicating your thoughts?"

Each of the three questions will be scored on a 4-point scale (1, Not at all; 2, A little; 3, Quite a bit; 4, Very much), which will subsequently be linearly transformed to a 0–100-point scale.

6.14.1.4 EQ-5D-5L

EQ-5D-5L scores will be analyzed by another Department. Therefore, score derivation rules and details of statistical methods to be used for analyzing EQ-5D-5L scores will be provided in a separate document.

6.14.2 Statistical Methods

The analysis of PRO measures, except EORTC QLQ-BN20 outcomes will be performed on all ITT population, as well as in C-ITT, unless otherwise stated. However, the analysis of EORTC QLQ-BN20 outcomes will be performed only on C-ITT.

A summary table on compliance measures will be provided for each PRO measure (EORTC QLQ-C30, EORTC QLC-LC13 and the 3 questions specific to CNS metastases (a part of EORTC QLQ-BN20 questionnaire) on ITT. The following will be displayed by visit:

- Number and percentage of subjects who filled out a questionnaire at a visit

- Summary statistics (median, minimum and maximum) of the percentage of questions answered for each questionnaire by visit.

The percentage for baseline will be calculated based on ITT population, except for the QLQ-BN20, the percentage for baseline will be calculated based on C-ITT population. For treatment visits, the denominator will be the number of subjects that are known to be alive, without progressive disease (as per investigator) and still in the study at the timepoint.

The scale score and change from baseline for each PRO measure will be summarized for each visit and by treatment group using descriptive statistics as well as the proportion of patients with improved, stable, or worsened outcomes.
For analysis of functioning domains and global QOL, a patient will be classified as improved if a 10-point or greater increase is observed in the average change from baseline scores across all available time points on FTP for that patient. Similarly, a patient will be classified as worse if a decrement of 10 points or worse is observed in the average change from baseline scores across all available time points for an individual patient. For analysis of symptom domains and single items, the classification into improved/worse categories is the reverse, such that a patient will be classified as improved if a decrement of 10-point or worse is observed in the average change from baseline scores across all available time points and will be classified as worse if a 10-point or greater increase is observed. For analysis of symptom domains and single items, a positive change indicates worsening (i.e., greater symptom severity) and a negative change indicates symptom improvement. Improvement and worsening rates between treatments will be compared using the Chi-Square test. Bar Charts will be generated for both improvement and worsening separately for each PRO measure. All scales for a specific PRO measure will be displayed on the same bar chart, as well as the 2 treatment arms.

Selected single and multi-item subscales (e.g. cough, chest pain (single item), dyspnea (single item and multi-item subscales), pain in arm/shoulder and fatigue, as measured by the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core (QLQ-C30) and the supplemental lung cancer module (QLQLC13), as well as the composite of three following symptoms (cough, dyspnea (multi-item subscales QLQ-LC13) and chest pain) will be presented graphically and will display the mean and standard error over time for each visit by treatment group.

Longitudinal analyses will be conducted to investigate the change from baseline in QLQ-C30 and EORTC QLC-LC13 scale score over the course of the first treatment period using linear mixed models. These models will be applied in ITT population. A linear mixed model will be fitted on the change from baseline in scale score including as:

- Explained variable: change in PRO measure scale score from baseline
- Fixed Effect: time, treatment arm, interaction between treatment and time, baseline value of the PRO measure scale score and the stratification factors. Time will be considered as a categorical variable.
- Random Effect: Patient

As a first approach, an unstructured correlation matrix will be used to model the correlation within patients.

The following SAS code will be used:

```
PROC MIXED DATA= dataset;
CLASS patient_id treat time strate1 strate2;
```

```
MODEL change_score = time treat time*treat baseline_score strate1
strate2/ solution ddfm=kr;
REPEATED time/subject=patient_id type=cs;
LSMEANS treat/cl diff;
RUN;
* change_score represents the change from baseline;
* treat represents the treatment group;
* strate1, strate2 represents the 2 categorical covariates related to
stratification factors as per eCRF;
* baseline_score represents all the score at baseline;
Further options to control the output may be added.
```

The following results will be presented for each PRO measure scale score:

- The least squares mean (LSMEANS) estimates by treatment,
- The difference in least squares means and their associated 95% CIs

Graphical representation of the difference in LSMEANS by treatment arm and 95% confidence interval will be created for each PRO measure.

To guard against a non convergence of the linear mixed model, the modelization of the treatment effect will include only the timepoints in FTP which have at least 3 non-missing observations in each treatment group.
All the above analysis will be repeated on C-ITT. Analysis related to QLQ-BN20 questionnaire will be performed on C-ITT only.

Time to Deterioration:
Time to deterioration in patient-reported lung cancer symptoms of each of the individual symptoms: cough (single item QLQ-LC13) , chest pain (single item), dyspnea (single item (QLQ-C30) and multi-item subscales (QLQ-LC13)), pain in arm/shoulder (single item subscales QLQ-LC13) and fatigue (multi-item subscales QLQ-C30) , as measured by the EORTC QLQ-C30 and the supplemental lung cancer module (QLQLC13), as well as for the composite of the three following symptoms: cough, dyspnea (multi-item subscales QLQ-LC13) and chest pain will be analyzed as a time-to-event endpoint as described for PFS. However, only descriptive statistics using Kaplan Meier methods will be provided, i.e. hazard ratio, log-rank test and estimated Kaplan Meier rate will not be provided.

Score of EORTC QLQ-C30, EORTC QLC-LC13 and the 3 questions specific to CNS metastases (a part of EORTC QLQ-BN20 questionnaire) scales will be listed.

Time to Permanent Deterioration:
Time to permanent deterioration in patient-reported lung cancer symptoms will be analyzed using the same methods as described for time to deterioration.

A permanent deterioration is defined as an increase in a score ≥ 10 points above baseline which must be held for at least two consecutive assessments or an initial score increase of ≥ 10 points which is followed by death within 3 weeks.

6.15 BIOMARKER ANALYSIS

The biomarker analyses are defined in a separate document for biomarker analysis plan (BAP).

6.16 MISSING DATA

Imputation of missing values for efficacy endpoints is provided in Section 6.11.

Imputation of partial/missing death date will be done as follows:

- If the date is completely missing, then the day of "Last known to be alive" +1 will be used
- If only day is missing and year and month are same as "Last known to be alive", then the day of "Last known to be alive"+1 will be used otherwise the 1st day of the month will be used
- If day and month are missing and year is same as "Last known to be alive", then the "Last known to be alive"+1 will be used, otherwise 1st of January will be used

Partially missing dates for adverse events (AEs) will be imputed as follows. Of note, imputation of missing/partial AE date will be done only to identify treatment emergent AEs.

AE onset dates

- Partially missing onset dates will be imputed as follows
    - When only Day is missing :
        - If Month & Year of the onset date are the same as Month & Year of first day of treatment in FTP/PPTP, the imputed onset date will be imputed as the minimum of first day of treatment in FTP/PPTP and the AE resolution date (imputed if needed).
        - Otherwise, the missing day will be replaced by "1".
    - When Day & Month are missing:
        - If Year of the onset date is the same as Year of first day of treatment in FTP/PPTP, the imputed onset date will be imputed as the minimum of first day of treatment in FTP/PPTP and the AE resolution date (imputed if needed).
        - Otherwise, the missing Day & Month will be replaced by "01JAN".

- Complete missing onset dates for AEs will be imputed by first day of treatment in FTP/PPTP and the AE will be considered as treatment emergent, unless the end date of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the year of the first day of treatment in FTP/PPTP.

AE resolution dates

- Incomplete resolution dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete resolution date.
- In all other cases the incomplete resolution date will not be imputed.

Partially missing dates for medications and procedures will be imputed as follows. Of note, imputation of missing/partial medications/procedures date will be done only to identify concomitant medications/procedures.

- If the start date of the medication/procedure is unknown (i.e. complete missing date) and there is no end date, the worst-case scenario will be assumed. The medication/procedure will be considered as both a prior medication/procedure and a concomitant medication/procedure for both treatment periods. In case there is an unknown start date but the end date is

known and is prior to the first day of treatment in FTP/PPTP, then the medication/procedure will not be considered as concomitant for the first treatment period/post-progression treatment period.

- If the month and the day of the start date of the medication/procedure are missing and there is no end date, the month and the day will be imputed to January, 1st of the year specified. In case the month and the day of the start date are unknown but the end date is known and is prior to the first day of treatment in FTP/PPTP, then the medication/procedure will not be considered as concomitant for the first treatment period /post-progression treatment period.
- If the day of the start date of the medication/procedure is missing and there is no end date, the day will be imputed to the first day of the month specified. In case the day of the start date is unknown but the end date is known and is prior to the first day of treatment in FTP/PPTP, then the medication/procedure will not be considered as concomitant for the first treatment period/post-progression treatment period.
- If the end date is unknown (i.e. missing), the date will be imputed to December, 31st 2099.
- If the month and the day of the end date of the medication/procedure are missing, the month and the day will be imputed to December, 31st of the year specified.
- If the day of the end date of the medication/procedure is missing, the day will be imputed to the last day of the month specified.

No other dates will be imputed, unless otherwise specified. The original incomplete or missing dates will be presented in the listings, not the imputed dates.

6.17 INTERIM ANALYSES

No interim analyses for efficacy or futility are planned.

7. REFERENCES

[1] Kohl, M (2015), “PSHREG: A SAS macro for proportional and nonproportional subdistribution hazards regression”, Computer Methods and Programs in Biomedicine, 118, 218-233

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[3] Watkins, C., Huang, x., Latimer, N., Tang, Y. and Wright, E. J. (2013), Adjusting overall survival for treatment switches: commonly used methods and practical application. Pharmaceut. Statist., 12: 348–357.