NOVARTIS

Global Medical Affairs

Ceritinib (LDK378)

Protocol CLDK378A2407 / NCT02465528

A Phase II, open label, multi-center, multi-arm study of ceritinib in patients with advanced solid tumors and hematological malignancies characterized by genetic abnormalities of anaplastic lymphoma kinase (ALK)

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List of abbreviations

ADME	Absorption Distribution Metabolism and Excretion
AE	Adverse Event
ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical Classification System
AUC0-24h	Area Under the Curve 0-24 h
b.i.d.	*bis in diem*/twice a day
BLRM	Bayesian Logistic Regression Model
BP	Blood pressure
BSC	Best supportive care
BUN	Blood Urea Nitrogen
Ca	Calcium
CABG	Coronary artery bypass graft
CBC	Complete blood count
CHF	Congestive heart failure
CI	Confidence Interval
CL	Clearance
Cmax	Maximum Concentration
CNS	Central Nervous System
CPK	Creatine phosphokinase
CR	Complete Response
CrCl	Creatinine clearance
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident
CYP	Cytochrome P
DLs	dose levels
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DS&E	Drug Safety and Epidemiology
e.g.	for example

[redacted]

ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EOT	End of Treatment
FDA	Food and Drug Administration
FAS	Full Analysis Set
FFPE	Formalin fixed paraffin embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyltranspeptidase
GI	Gastrointestinal
GLP	Good laboratory practice
GM-CSF	Granulocyte macrophage colony-stimulating factor
GVHD	Graft-versus-host disease
HBV	Hepatitis B Virus
hCG	human chorionic gonadotropin
HCV	Hepatitis C Virus
HDL	High density lipoprotein
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hr	hour
IB	Investigators Brochure
IC50	Half maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IMT	Inflammatory Myofibrolastic Tumor
IMWG	International Myeloma Working Group
IN	Investigator notification
INR	International Normalized Ratio
IUD	intrauterine device
IUS	intrauterine system
i.v.	intravenous(ly)
IWG	International working group
KA	Keratoacanthoma
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
mg	milligram
MI	Myocardial infarction

MIGB	Metaiodobenzylguanidine
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NA	Not applicable
Na	Sodium
NCI CTC	National Cancer Institute Common Terminology Criteria
nM	Nano molar
NSCLC	Non-small cell lung carcinoma
OC	Oral contraception
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD	Pharmacodynamics
PE	Pulmonary embolism
PET	Positron emission tomography
PFS	Progression –free survival
PHI	Protected health information
PK	Pharmacokinetics
PLT	Platelets
PR	Partial Response
POC	Proof of Concept
PT	Prothrombin time
QD	*quaque die*/once a day
QTc	QT corrected
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
RANO	Respone assessment in neuro-oncology
SAP	Statistical Analysis Plan
RAS	RAS oncogene (rat sarcoma viral oncogene homologue)
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase two dose
RTK	Receptor tyrosine kinase
SAE	Serious Adverse Event
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic
SOP	Standard Operating Procedure
SPEP	Serum protein electrophoresis
SUSAR	Suspected unexpected serious adverse reaction
TdP	Torsade de Pointes
TIA	Transient ischemic attack
Tmax	The time at which the maximum observed concentration (Cmax) occurs

TSH	Thyroid stimulating hormone
ULN	Upper Limit of Normal
UPEP	Urine protein electrophoresis
WBC	White Blood Cell
WHO	World Health Organization
WNL	Within normal limits

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason

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Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

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Amendment 1

Amendment rationale

This global amendment clarifies the inclusion critieria #2 for ALK positivity. A patient must have a histologically or cytologically confirmed diagnosis of one of the tumors that is ALK positive (ALK+). The ALK test results must be available at the investigator site before the first dose of the study drug.

The tumor types are described below:

Anaplastic Large Cell Lymphoma (ALCL), local confirmation of diagnosis of ALK+ ALCL is sufficient for eligibility.

Inflammatory Myofibroblastic Tumor local confirmation of translocation involving the ALK gene.

Glioblastoma, Inflammatory breast cancer and any other locally documented ALK+ tumor must carry a locally documented genetic alteration of ALK including any of the following:

- A known activating mutation in the kinase domain of ALK or a point mutation in the kinase domain of ALK that results in an amino acid change that has not been reported in normal germline DNA, or any other mutation (e.g. insertion or deletion) which results in a change in the amino acid sequence of the kinase domain of ALK, as long as the alteration does not clearly result in inactivation of the kinase activity, such as deletion of the kinase domain, or a stop codon preventing translation of the kinase domain.
- An amplification of the ALK gene, defined as ≥ 6 copies per cell, or 3 copies per haploid genome. When assessed by FISH, ALK amplification must be observed in focal clusters of tumor cells (not only single cells) or in more than one-third of the tumor cells.
- A translocation involving the ALK gene.
- Glioblastoma patients only, overexpression of ALK protein documented locally is also acceptable for eligibility

This amendment also provides follow up evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases. Additioanlly, the following changes were made for consistency with other Novartis sponsored clinical studies:

- Updated the exclusion criteria for contraception use
- Dose guidance modification for QTcF text was updated to provide clarification on monitoring procedure.

Changes to the protocol

- List of Abbreviations: deleted the duplicate terms: DLT, IB, IC50, ICF, ICH, SD and SGOT. Added the term POC, DILI, IMTand MIGB
- [redacted]

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- Protocol Summary: inclusion criteria# 2 has been modified to provide additional information for the types of ALK gene activating/alteration (and/or overexpression.
- Protocol Summary: inclusion criteria #7 ALCL by Cheson for the measurement of a nodal has been corrected to ≥ 1.5 cm.
- Protocol Summary: inclusion criteria #8, calculated creatinine clearance has been corrected to ≥ 30 mL/min
- Protocol Summary: exclusion criteria #10, has been modified to QTcF > 470 msec (as means of triplicate ECGs) at screening.
- Protocol Summary: Updated the interim analysis section.
- Section 1.2.1: Updated the approval/submission status of certinib.
- Section 1.2.1.1.4: corrected references to the appropriate inclusion and exclusion criteira.
- [redacted]
- [redacted]
- Section 4.1: Table 4-2; Deleted reference to FISH in the table heading.
- Section 4.2: Removed “at least” wording.
- Section 4.2: Deleted the sentence referring to a separate charter.
- Section 5.2: inclusion criteria #2 has been modified to provide additional information for the types of ALK gene that will be acceptable for the 5 tumor types.
- Section 5.2: inclusion criteria #7 ALCL by Cheson for the measurement of a nodal has been corrected to ≥ 1.5 cm.
- Section 5.2: inclusion criteria #8 calculated creatinine clearence has been corrected to ≥ 30 mL/min
- Section 5.2: exclusion criteria #10, has been modified to QTcF > 470 msec (triplicate ECGs) at screening
- Section 6.2.7.2: added additional guidelines for Hy’s Law for the follow-up of laboratory liver abnormalities.
- Table 6-3: AST and ALT provided a reference to Section 6.2.7.2
- Table 6-3: provided clarification for pancreatic toxicity.
- Table 6-3: provided additional guidance for QTc dose modifications.
- Section 6.3.1.1: clarified corticosteroid treatment guidance.
- Table 7-1: added a visit name to ensure documentation of local ALK testing resultsare available at screening to the investigator.
- Table 7-1: included ECG and vital sign measurements at C1 Day 15 and C2 Day 15.
- Table 7-1: clarified the timing of the radiological tumor assessments (MRI/CT/PET/PET-CT).
- Table 7-1: clarified the need to perform bone marrow aspirate or biopsy at screening and EOT.
- Table 7-2: corrected “follow-up” to EOT.

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- Table 7-2: clarified radiological procedure for GMB patients.
- Section 7.3.2.2: Corrected “respirations” to respiratory rate.
- Section 7.3.2.4: Corrected the timing interval.
- Section 7.3.2.5: Deleted the reference to a central lab for the analysis of out of rangeurine samples.
- Section 7.3.2.6.1: added the triplicate ECGs at screening
- Table 7-6: corrected the unit of measure for tumor slides from uM to µm.
- 10.5.3.3: Changed the reference from “RAP” to“SAP”.
- 10.5.3.4: Changed the reference from “RAP” to“SAP”.
- 10.6.1: Removed reference to “PD”.
- 10.7: Updated this section to include all available data in the interim analysis.
- Corrected discrepancies, typographical errors or add missing minor information.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

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Protocol Summary

Protocol number	CLDK378A2407
Title	A Phase II, open label, multi-center, multi-arm study of ceritinib in patients with advanced solid tumors and hematological malignancies characterized by genetic abnormalities of anaplastic lymphoma kinase (ALK)
Brief title	Ceritinib Rare Indications Study in ALK+ Tumors
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This Proof-of-Concept (POC) efficacy study will assess the preliminary antitumor activity and safety and tolerablity using ceritinib (LDK378) in the treatment of life threatening tumors that are characterized by ALK genetic alteration (and/or overexpression in some diseases). The tumors selected in this study are Anaplastic Large Cell Lymphoma (ALCL), Inflammatory Myofibroblastic Tumor (IMT), Glioblastoma (GBM), Inflammatory Breast Cancer or any other ALK+ tumor type refractory or intolerant to standard therapeutic treatments. The tumor pathogenesis may involve ALK gene aberration resulting in potential dysregulation at the protein level. Inhibition of dysregulated protein by ALK inhibitors such as ceritinib is a rational approach to inhibit ALK-driven proliferation.
Primary Objective	To assess the preliminary antitumor activity of ceritinib treatment in patients with life threatening diseases other than NSCLC known to be associated with ALK dysregulation following failure or intolerance of the standard therapy. The antitumor activity will be measured by Disease Control Rate (DCR) based on local investigator assessment. For patients with solid tumors the assessment criteria will be RECIST 1.1. For GBM, RANO and RECIST 1.1 criteria will apply. For hematologic tumors, Cheson response criteria will apply. The DCR is defined as the proportion of ceritinib treated patients with complete response (CR), partial response (PR) or stable disease (SD) at 16 weeks from the start of the treatment. The DCR responses will need to be confirmed at least 4 weeks later by the same method
Secondary Objectives	• To assess the antitumor activity of ceritinib as measured by ORR, DOR, TTR as determined by investigators • To assess the antitumor activity of ceritinib as measured by PFS determined by investigators • To assess the safety and tolerability of ceritinib. Hematology, biochemistry, urinalysis, coagulation, pregnancy test, hormones (males only); ECG; Performance status; Physical examination; Vital signs; Adverse events will be assessed using CTCAE 4.03.

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Study design	This is a phase II, open-label, multi-center, multi-arm POC study to assess the preliminary anti-tumor activity and safety and tolerability of ceritinib in diverse populations of patients suffering from life threatening advanced, malignant diseases (solid tumors other than NSCLC) and hematological malignancies associated with ALK dysregulation contributing to the disease phenotype (see Table 4-2)
Population	Approximately 106 male and female patients 18 years and older.
Inclusion criteria	1. Written informed consent obtained prior to any **screening** procedure 2. Patient must have a histologically or cytologically confirmed diagnosis of one of the tumors that is ALK positive (ALK+). The ALK test results must be available at the investigator site before the first dose of the study drug. The tumor types are described below: **Anaplastic Large Cell Lymphoma (ALCL)**, local confirmation of diagnosis of ALK+ ALCL is sufficient for eligibility. **Inflammatory Myofibroblastic Tumor** locally documented translocation involving the ALK gene, **Glioblastoma, Inflammatory breast cancer Any other locally documented ALK+ tumor.** Must carry a locally documented genetic alteration of ALK including any of the following (ALK overexpression is also acceptable in Gliobalstoma): • A known activating mutation in the kinase domain of ALK or a point mutation in the kinase domain of ALK that results in an amino acid change that has not been reported in normal germline DNA, or any other mutation (e.g. insertion or deletion) which results in a change in the amino acid sequence of the kinase domain of ALK, as long as the alteration does not clearly result in inactivation of the kinase activity, such as deletion of the kinase domain, or a stop codon preventing translation of the kinase domain. • An amplification of the ALK gene, defined as ≥ 6 copies per cell, or 3 copies per haploid genome. When assessed by FISH, ALK amplification must be observed in focal clusters of tumor cells (not only single cells) or in more than one-third of the tumor cells. • A translocation involving the ALK gene. • Glioblastoma patients only, overexpression of ALK protein documented locally is also acceptable for eligibility 3. Patient must provide an archival or fresh tumor tissue before the first dose of the study drug for potential retrospective ALK testing at a Novartis designated central laboratory by a comparative technology: • the confirmation of ALK positivity is not required for enrollment if other inclusion and exclusion criteria are fulfilled 4. Patient is 18 years or older at the time of informed consent.

[redacted]

	5. Patient has WHO Performance Status (PS) ≤ 2 6. Patient must have received at least one line of prior systemic treatment for recurrent, locally advanced and/or metastatic disease, may have discontinued for: • Disease progression as defined by RECIST 1.1 for solid tumors; by RANO and RECIST for GBM and by Cheson assessment criteria for lymphoma • Intolerance described as any discontinuation due to an AE of any grade despite appropriate supportive treatment 7. Patient must have a wash-out period prior to the first dose of ceritinib: • Chemotherapy, immunotherapy, stem cell transplant within 4 weeks • Radiotherapy and ALK inhibitors must have discontinued within 1 week • Recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v4.03). Exception to this criterion: patients with any grade of alopecia are allowed to enter the study. 8. Patient has at least one measurable lesion as defined by appropriate guidelines. A lesion at a previously irradiated site may only be counted as a target lesion if there is clear sign of progression since the irradiation. • Solid Tumors: by RECIST 1.1 (Section 14.2) • GBM: by RANO and RECIST (Section 14.3 and Section 14.2) • ALCL: by Cheson (Section 14.4). Patient has at least one measurable nodal lesion (≥1.5). In case where the patient has no measurable nodal lesions ≥ 1.5 cm in the long axis at screening, then the patient must have at least one measurable extra-nodal lesion. 9. Patient must meet the following laboratory values at the screening visit: • Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L; • Platelets ≥ 75 x 10^9/L • Hgb ≥ 8 g/dL • International Normalized Ratio (INR) ≤ 1.5 • Serum creatinine ≤ 1.5 mg/dL and/or calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 30 mL/min; • Total bilirubin ≤ 1.5 x upper limit of normal (ULN), except for patients with Gilbert's syndrome, who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN; • Aspartate transaminase (or aminotransferase; AST) ≤ 2.5 x ULN, except for patients with liver metastasis, who are only included if AST ≤ 5 x ULN; • Alanine transaminase (or aminotransferase; ALT) ≤ 2.5 x ULN, except for patients with liver metastasis, who are only included if AST ≤ 5 x ULN; • Alkaline phosphatase (ALP) ≤ 5.0 x ULN. • Serum amylase ≤ 2 x ULN • Serum lipase ≤ ULN • Fasting plasma glucose ≤175 mg/DL (≤9.8 mmol/L)

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	10. Patient must have the following laboratory values within ≤ Gr1 (CTCAE v4.03) at screening: • Potassium • Magnesium • Phosphorus • Total calcium (corrected for serum albumin) 11. Patient must be willing and able to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.
Exclusion criteria	1. Patient with ALK+ lung cancer. 2. Patient with known hypersensitivity to any of the excipients of ceritinib (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate). 3. Patient with symptomatic CNS metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms. 4. Patient with history of carcinomatous meningitis 5. Patient with diarrhea CTCAE ≥ grade 2; or patients with neuropathy CTCAE ≥ grade 2 6. Patient with acute or chronic GI disease that may significantly alter the absorption of ceritinib 7. Patient with a history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease 8. Patient has history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis 9. Presence or history of a malignant disease other than primary tumor under consideration that has been diagnosed and/or required therapy within the past 3 years. • Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type 10. Patient has clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months) such as: • unstable angina within 6 months prior to screening; • myocardial infarction within 6 months prior to screening; • history of documented congestive heart failure (New York Heart Association functional classification III-IV); • uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication • initiation or adjustment of antihypertensive medication(s) is allowed prior to screening; • ventricular and atrial arrhythmias; supraventricular and nodal arrhythmias not controlled with medication; • Other cardiac arrhythmia not controlled with medication. • Corrected QT (QTcF) >470 ms using Fridericia's correction on the screening ECG (as mean of triplicate ECGs). 11. Evidence of active viral hepatitis, including Hepatitis A, B or C (testing for viral hepatitis is not mandatory). 12. Known diagnosis of human immunodeficiency virus (HIV) infection

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	(HIV testing is not mandatory). 13. Patient receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with ceritinib and for the duration of the study: • Strong inhibitors or strong inducers of CYP3A4/5 • Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5 and/or CYP2C9 • Medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes 14. Patient who are currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants. 15. Patient receiving unstable or increasing doses of corticosteroids. • If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms (non-CNS), dose must have been stabilized (or decreasing) for at least 5 days before first dose of study treatment. 16. Patient receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of study treatment, and for the duration of the study. Patients on non-enzyme-inducing anticonvulsants are eligible. 17. Major surgery (e.g., intrathoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting study treatment or who have not recovered from side effects of such procedures. 18. Pregnant or nursing (lactating) women 19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and for 3 months after stopping medication. Highly effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment • Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject • Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. • In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking

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	study treatment. 20. Sexually active male unless they use a condom during intercourse while taking the drug and for 3 months after the last dose of ceritinib treatment. Male patients should not father a child for 3 months after the last dose of ceritinib treatment. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid 21. Patient has other severe, acute, or chronic medical or psychiatric conditions including uncontrolled diabetes mellitus or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results.
Investigational and reference therapy	Ceritinib (LDK378) 750 mg once daily oral. No reference therapy will be administered in this trial.
Efficacy assessments	**Efficacy assessments will be performed every 8 weeks:** **Primary objective:** To assess **Disease Control Rate (DCR)** associated with ceritinib treatment based on local investigator assessment For patients with solid tumors the assessment criteria will be RECIST 1.1. For GBM, RANO and RECIST 1.1 criteria will apply. For hematologic tumors, Cheson response criteria will apply. DCR will include complete response (CR), partial response (PR) or stable disease (SD) at 16 weeks since the start of the treatment. The DCR responses will need to be confirmed at least 4 weeks later by the same method. **Secondary objectives:** • To assess **Overall Response Rate (ORR)** based on local investigator assessment • To assess **Duration of Response (DOR)** based on local investigator assessment • To assess **Time to Response (TTR)** based on local investigator assessment • To assess **Progression-Free Survival (PFS)** based on local investigator assessment

Safety assessments	Adverse Events (AEs) using Adverse Events CTCAE 4.03 including:
	• Serious AEs (SAEs)
	• Laboratory profiles
	  • hematology
	  • biochemistry
	  • urinalysis
	  • coagulation
	  • pregnancy test (females)
	  • hormones (males only)
	• Physical examination
	• Vital signs
	• Electrocardiograms (ECG)
	• WHO Performance Assessment

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Data analysis	The primary endpoint of this study is to assess Disease Control Rate (DCR) defined as the proportion of patients with CR, PR and stable disease (SD) lasting at 16 weeks since the start of treatment based on local investigator's assessment according to RECIST 1.1., RANO or Cheson hematological criteria. Responses must be confirmed at least 4 weeks later by the same method. DCR will be analyzed using Bayesian hierarchical model. Posterior summary (point estimate and 95% credible interval) and posterior probability of not being clinically meaningful for each arm (tumor type) will be calculated. For a specific arm, a POC about treatment with ceritinib will be declared if both of the following conditions are met: • Observed DCR > clinically meaningful threshold (Table 1 see Section 10 for more details) • Posterior probability of not being clinically meaningful (Table 1 see Section 10 for more details) is less than 20% As a sensitivity analysis DCR and its 95% confidence interval will also be provided based on exact binomial distribution. **Statistical analysis of the secondary endpoint:** The secondary endpoints of this study are: ORR (investigator-assessed); defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) based on local investigator's assessment according to RECIST 1.1, RANO or Cheson hematological criteria. ORR will be analyzed using Bayesian hierarchical model. Posterior summary (point estimate and 95% credible intervals) and posterior probability of different categories of interests will be provided. As a sensitivity analysis ORR and its 95% confidence interval will also be provided based on exact binomial distribution. For each tumor type, duration of response (DOR) and time to response (TTR) will be described in tabular and graphical format using Kaplan-Meier methods. The Kaplan-Meier estimate of the distribution function will be constructed. The number of patients at risk at certain time points will be shown on the plot. The estimated median (in weeks) along with 95% CIs, as well as 25th and 75th percentiles will be reported. Median PFS which will be estimated using the Kaplan-Meier method and will be presented along with 95% confidence interval in each disease group. **Interim Analysis** Interim analysis for each arm (tumor type) will be performed for decision making (early stopping or continuation of recruitment) when a predefined number of patients (5 for IMT and 10 for all other tumor types) have completed 16 weeks of treatment with ceritinib and have their anti-tumor activity assessed. Responses observed at week 16 (CR or PR) must be confirmed by a subsequent assessment at least 4 weeks later. The reduced number of patients (5) in the IMT arm is based on the rare

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incidence of this tumor type. All available data will be used for analysis at the interim. However, a decision will be made only for arm with minimum number of pre-specified patients (a minimum of 5 patients in IMT arm or a minimum of 10 patients for any of the other arm). For a specific arm, a decision will be made based on the calculated probability as given below:

- If the posterior probability of being clinically meaningful (Table 1) is less then 20% then recruitment will be stopped in that arm
- Otherwise, recruitment will be extended for at least 10 more patients in that arm (including IMT).

Depending on enrollment and follow-up, there may be multiple interim analyses.

Sample size calculation:

The study will enroll patients in 5 parallel arms from at least 4 tumor types, with each tumor type having different cutoff for being clinically meaningful as shown on Table 1. The 5th arm will enroll any other ALK+ tumor. If there are minimum 5 patients of the same tumor type in the "Any other ALK+ tumor" arm, then a separate arm will be opened for that specific tumor type. The study plans to enroll a minimum of 5 patients in IMT arm and a minimum of 10 patients in each of the other 4 arms. The primary analysis will be performed separately for each arm when both initial accrual and the accrual following-up the interim analysis are complete in an arm. For each of the arm the effect of ceritinib is defined as clinically meaningful based on the threshold for observed DCR (Table 1).

Table 1: Type of diseases of interest with definition of being clinically meaningful

Disease Code	Arm (Tumor Type)	#Patients† at Interim	DCR Not Clinically meaningful	DCR Clinically meaningful
T1	Anaplastic large cell lymphoma (ALCL)	10	<40%	≥50%
T2	Inflammatory myofibroblastic tumor (IMT)	5	<20%	≥30%
T3	Glioblastoma	10	<10%	≥20%
T4	Inflammatory breast cancer	10	<10%	≥20%
T5	Any other ALK+ tumor tumor)	10	<10%	≥20%

† Extend recruitment for at least 10 more patients in each arm according to IA outcome [p(clinically meaningful)>20%].

A Bayesian hierarchical model (BHM) will be applied to estimate the DCR, for each arm, and its 95% credible interval and posterior probability of being clinically meaningful. The proposed model is a modified version of standard model which assumes full exchangeability (similarity) between the disease-specific response rates. The proposed model is robust as it allows for non-exchangeability (non-similarity) for each disease group. This approach allows the data to determine the strength of

[redacted]

	borrowing across the strata in a flexible way. Allowing for an estimated attrition rate of 10%, a total of approximately 106 patients will be enrolled in order to get 95 patients for the final analysis.
Key words	Anaplastic large cell lymphoma (ALCL); Inflammatory myofibroblastic tumor (IMT); glioblastoma multiforme (GBM); inflammatory breast cancer (IBC); ALK inhibitor; ALK+ tumor, ceritinib

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Anaplastic lymphoma kinase gene (ALK) has emerged as a strong biomarker and therapeutic target for cancer patients who may benefit from ALK-targeting agents. Aberrant ALK has oncogenic potential and activates variety of intracellular signaling pathways. The key signaling pathways are (1) Janus kinase 3 (JAK3)-STAT3 intracellular pathway; (2) phosphoinositide 3-kinase (PI3K)-Akt pathway and (3) RAS extracellular signal regulated (ERK) pathway (Enrique 2011). Overexpression and activation of ALK mediate many downstream effects that may contribute to transformation, increased proliferation, and increased survival.

Activation of ALK appears to be a molecular oncogenic event that is seen in most diverse tumors such as NSCLC, ALCL, IMT, neuroblastoma, or other hematologic and solid tumors. All tumors bearing genetic aberrations (e.g. ALK mutations, amplification, translocation) or showing overexpression of the ALK protein, might potentially benefit from ALK inhibitors.

Anaplastic large cell lymphoma (ALCL)

The ALK gene was first described in anaplastic large cell lymphoma (ALCL) an aggressive mature T-cell lymphoma that accounts for 10%–15% and 2%–8% of non-Hodgkin lymphomas in children and adults, respectively (Merkel 2011). ALK was

identified as the gene on chromosome 2 fused to the NPM gene in the t(2;5)(p23;Q35) translocation. Other fusion partners have been described in ALCL (e.g. TFG, MSN, CLTC and ATIC), but NPM-ALK accounts for more than 75-80% of all ALK+ ALCL cases and is found in approximately half of patients with ALCL, and a majority of pediatric ALCL cases (Gascoyne 1999, McDermott 2008, Savage 2008). ALK activation in ALCL is associated with activation of various signal transduction intermediates and pathways implicated in oncogenesis, including STAT3, Grb2, mTORC1, PI3K/AKT, and MEK/ERK (Tabbo 2012).

The first-line therapy for adult patients with systemic ALCL is a multi-agent, anthracycline-containing regimen, in most cases CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). In patients with refractory or relapsed ALCL, there is no established standard treatment and therapeutic options are limited, as only a few agents have shown consistent activity. Despite various protocols, ALCL in pediatric and adolescent patients still has a relapse rate of 25%–30%. The therapies for refractory or relapsed disease are highly variable with no established standard (Le Delay 2008). ALCL patients are encouraged to participate in clinical trials to establish standard treatment in the setting of refractory or relapsed disease as well as to develop new therapeutic strategies (Xueyan 2014)

ALK activation by translocation, amplification, point mutations, or other genetic rearrangements has since been identified in other malignancies.

[redacted]

Non-small cell lung cancer (NSCLC)

About 2-8% of non-small cell lung cancers (NSCLC) carry activating translocations of ALK, most commonly an EML4-ALK translocation created by an intrachromasomal inversion in chromosome 2 (Soda 2007, Scagliotti 2012, Takeuchi 2009). Two ALK inhibitors have been developed for treatment of NSCLC.

- Crizotinib (Xalcori™) was approved in the USA by the Food and Drug Administration (FDA) in August 2011 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (*ALK*)+ as detected by an FDA-approved test., primarily based on response rates of 50% from the first 136 patients with *ALK*-rearranged NSCLC enrolled on PROFILE 1005 and secondarily on a response rate of 61% from the first 119 patients with *ALK*-rearranged NSCLC enrolled on PROFILE 1001 (Camidge 2011). Crizotinib has since been approved in many other countries worldwide.
- Ceritinib (Zykadia ™) was approved by the FDA in April 2014 for the treatment of patients with anaplastic lymphoma kinase-positive (ALK+) metastatic non-small celllung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The approval of ceritinib is based on a pivotal trial that included 163 patients with metastatic ALK+ NSCLC who progressed on or were intolerant to treatment with crizotinib. Among previously-treated patients, ceritinib achieved an overall response rate (ORR) of 54.6% [95% CI, 47-62%] and a median duration of response (DOR) of 7.4 months [95% CI, 5.4-10.1 months]. (Shaw 2014). Ceritinib has been approved and is undergoing regulatory approval in many other countries worldwide.

Inflammatory myofibroblastic tumors (IMT)

Half of inflammatory myofibroblastic tumors (IMT), a rare soft tissue sarcoma most commonly found in children, harbor genetic alterations of ALK, including translocations and changes in gene copy number (Coffin 2007, Griffin 1999). Several fusion partners have been identified. Two related tropomyosin genes TPM3 and TPM4 are the most common translocation partners for ALK in IMT and together with other fusion genes (e.g. CARS-ALK, RANBP2, CTLC1-ALK, SEC31L) constitutively activate ALK and induce transformation in cell lines and animal models (Lawrence 2000, Ladanyi 2000, Giuriato 2007). Butrynski et al (2010) reported sustained partial response to an ALK inhibitor (PF-02341066, crizotinib) in ALK+ IMT patient, whereas no observed activity was found in another patient without ALK translocation. Cessna described abnormalites of chromosome 2p23 with expression of p80 and ALK1 in up to 40% of IMT's (Cessna 2002). These tumors may exhibit aggressive local behavior and rarely metastasis.

The primary therapeutic approach for IMT is surgery if the anatomic location is amenable to a resection. If surgery is not possible, these lesions are typically treated with a variety of regimens including radiation and chemotherapeutic agents. Surgery as the standard of treatment, may be followed up by adjuvant chemotherapy and/or radiotherapy depending of the tumor aggressivness. Adjuvant therapy targeted at the more aggressive variants may prove to be warranted with the better understanding of the underlying genetic alterations.

Glioblastoma (GBM)

Human glioblastoma (GBM) is highly invasive and particularly aggressive primary brain tumor. Most patients diagnosed with this tumor die within one year from the diagnosis and only 5% survive more than 5 years despite aggressive therapies (CBTRUS 2011). Over the last decade, a variety of different treatments were explored with very limited success. Major challenges in therapy of GBM are associated with the location of the disease, its complex and heterogeneous biology and the blood-brain barrier that consequently prevents drug delivery to the brain parenchyma and the tumor itself (Kesari 2011).

ALK overexpression was found in human glioblastoma (GBM) relative to normal brain and ALK mRNA was detected in GBM cell lines (Powers 2002). In Glioblastoma the growth factor pleiotropin (PTN) activates ALK signaling and the PTN-ALK axis drives tumor growth suggesting that inhibition of ALK could be good therapeutic approach.

After initial therapy fails, therapeutic options are limited and generally not effective. There is no standard of care for recurrent GBM. Median time to progression at this stage is about 10 weeks and overall survival ~30 weeks (Wong et al 1999). Chemotherapy options have been and continue to be quite limited. Many agents have been used in this setting with rather disappointing results. Bevacizumab, an anti-VEGF inhibitor, has been approved by FDA for use in recurrent GBM in 2009 (Cohen et al 2009). The search for new agents and better clinical trial designs are highly recommended (Mrugala et al 2013)

Inflammatory breast cancer (IBC)

Inflammatory breast carcinoma (IBC) is a relatively rare (5% of all cases) form of breast cancer with distinct clinicopathologic features (Anderson 2003). IBC is characterized by an early age at diagnosis and poor survival outcome due to an aggressive clinical behavior. Despite advances in the multidisciplinary treatment, the prognosis is much less favorable than for other types of BC, with a 5-year survival ranging from 30% to 50% (Key 2001). There are currently no standard IBC-specific treatments for patients with advanced disease; therefore, enrollment in available clinical trials, including those of novel targeted therapies, is strongly recommended for IBC patients. The usual treatment of IBC is chemotherapy followed by surgery to remove the cancer. Radiation follows surgery. The use of anthracyclines (such as doxorubicin/Adriamycin® and epirubicin/Ellence®) and taxanes (such as paclitaxel/Taxol® and docetaxel/Taxotere®) as chemo drugs for IBC have been shown to improve outcomes. If the cancer is HER2-positive trastuzumab (Herceptin®) is given as well. If the cancer is hormone-receptor negative and HER2-negative (known as triple negative), the chemo drug carboplatin may be added to paclitaxel.

EML4-ALK fusion was found in 2.4% of breast cancers (Lin 2009). The presence of a mild increase in copy numbers has been noted in IBC. This is mostly due to increased copies of chromosome 2 rather than ALK gene amplifications (Krishnamurthy 2013). Other studies showed that ALK is amplified in most inflammatory breast cancer cases and crizotinib caused tumor shrinkage in mouse xenograft IBC (Tuma 2012). Although combined use of chemotherapy, surgery, and radiation therapy has somewhat improved disease-free and overall survival rates, there is still a strong need for new approaches one of which includes targeted systemic therapy.

[redacted]

Other ALK positive (ALK+) tumors

ALK activation is found in approximately 10% of neuroblastomas, but in contrast to ALCL and NSCLC, ALK activation in neuroblastoma occurs by point mutation (e.g. hotspot and gain-of-function mutations like F1174L and R1275Q) or ALK gene amplification (Chen 2008, Azarova 2011). Most pedigrees exhibiting the rare syndrome of familial neuroblastoma carry somatic mutations that result in ALK activation, indicating that ALK is an important driver in this disease (Mosse 2008).

Increased ALK protein expression and increased ALK gene copy number have also been described recently in 50%-80% of rhabdomyosarcomas, more often in the alveolar subtype than the embryonal subtype.

ALK rearrangements were identified in <1% of renal cell cancer (RCC) while ALK copy number gain was identified in 10% of RCC (Sukov 2012). ALK gene mutations were found in anaplastic thyroid cancer (ATC) with a prevalence of 11% but not in papillary (PTC) and follicular thyroid cancers (FTC) (Murugan 2011). TPM4-ALK has been recognized in the tumorigenesis of esophageal and other tumor types (Jazzi 2006). Further, translocations linking ALK to multiple fusion partners were subsequently identified in other malignancies. EML4-ALK fusion was found in 2.4% of colorectal cancer (Lin 2009).

In summary, the available treatments for the selected ALK+ tumors are scarse, ineffective and new treatment modalities to prolong patient's lives are needed.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of ceritinib

Ceritinib [5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2 (isopropylsulfonyl) phenyl]-2,4-pyrimidinediamine] is an orally available ALK inhibitor. Ceritinib is an approximately 20-fold more potent ALK inhibitor than crizotinib, more selective for ALK and does not inhibit MET.

In addition, ceritinib shows potent antitumor activity in crizotinib-resistant animal models (as described below), and the efficacy seen in the Phase I clinical trial in patients (with and without previous crizotinib therapy) led to the approval of ceritinib by the FDA under the trade name ZYKADIA™ on 29-Apr-2014 for the following indication:

- "Ceritinib (Zykadia ™) is indicated for the treatment of patients with ALK-positive)metastatic non-small cell lung cancer NSCLC who have progressed on or are intolerant to crizotinib.
  This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials."

Furthermore, the European Commission approved ZYKADIA on 06-May-2015 for the following indications:

[redacted]

ZYKADIA is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.

Submissions to other health authorities worldwide have been completed in some countries and are underway in others.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Pharmacology

Ceritinib inhibits ALK and ALK-mediated signaling pathways in a dose-dependent manner. It inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells both *in vitro* and *in vivo*. Ceritinib is approximately 20-fold more potent than crizotinib in enzymatic inhibition assays of ALK kinase activity In a kinase panel of 35 additional enzymes, ceritinib demonstrated a high degree of selectivity for ALK inhibition by inhibiting only 2 other kinases (INSR and IGF1R) but with approximately 50-fold less potency than ALK inhibition.

Inhibition of fusion oncogenes NPM-ALK and EML4-ALK in mouse and rat xenograft models resulted in inhibition of tumor growth and tumor regression in vivo. Ceritinib was also active in cell lines with ALK amplification or expression of activating point mutations.

1.2.1.1.2 Antitumor activity in xenograft models

Ceritinib is highly active in mouse and rat xenograft models of lung cancer and ALCL that carry an ALK rearrangement. In murine xenograft models of H2228 NSCLC and Karpas299 ALCL cells, ceritinib dosed at 25mg/kg daily, a dose below the maximum tolerated dose (MTD) in clinical studies, resulted in complete regression of established tumors.

Ceritinib also has potent antitumor activity against crizotinib-resistant H2228 NSCLC cell lines, including resistant variants carrying I1171T or C1156Y mutations in the ALK kinase domain. These data support the hypothesis that ceritinib may be clinically active in ALK-rearranged NSCLCs in multiple treatment settings.

1.2.1.1.3 Nonclinical pharmacokinetics (PKs) and metabolism

In general, ceritinib was moderately absorbed in rats (37%) and monkeys (≥40%). Oral bioavailability was complete in fed dogs, suggesting the possible existence of a positive food effect. The formulation used in these bioavailability determinations was a 0.5% methylcellulose suspension except for the mouse where a solution formulation was used. Ceritinib is highly bound to plasma protein (>94%) in all species. Following oral administration of [^{14}C] ceritinib to LEH male rats, radioactivity was widely distributed. The highest tissue exposures were found in intestine wall, uveal tract, pituitary gland, bile, adrenal cortex, harderian gland, liver, spleen, lymph node, lung, kidney, thyroid, bone marrow, adrenal medulla and pancreas (25- to 710-fold higher exposure relative to blood). Although the brain to blood concentration ratio of drug-related radioactivity was low compared to these other tissues with a brain-to-blood exposure (AUC_{inf}) ratio of approximately 15%, it was higher than the 3% background associated with brain vasculature at all monitored time points.

[redacted]

This indicates that drug-related radioactivity crossed the blood-brain barrier. Unchanged ceritinib was the major component in feces and bile of intact and bile duct-cannulated rats. In the rat, ceritinib underwent oxidation leading to the formation of four oxygenated metabolites (designated as M23.6, M30.6, M35.8, and M33.4). In addition, ceritinib underwent sulfation leading to M36.8 and oxidation followed by sulfation resulting in the presence of M29.5. Ceritinib also underwent glucuronidation leading to M26.8 and M27.6. The major metabolite in feces was designated M33.4 (oxygenation) accounting for approximately 7% of the dose. All other metabolites in feces and bile were minor (<5% of the dose). In rats dosed with [^{14}C] ceritinib, ceritinib -derived radioactivity was excreted predominantly via the fecal route (>99%), and renal excretion was a minor pathway for excretion (<1%). Fecal excretion was the result of biliary excretion (69%) and gastrointestinal (GI) secretion (31%). Since parent drug was the major component in bile and feces after intravenous (i.v.) administration, enterohepatic circulation may occur.

CYP3A4/5 is the major hepatic enzyme metabolizing ceritinib in a human *in vitro* system. The metabolic drug-drug interaction (DDI) potential of ceritinib as an inhibitor was evaluated using pooled human liver microsomes. Based on the assessment of clinical significance of in vitro results using the appropriate DDI decision tree described in FDA draft DDI guidance 2012 and EMA DDI guideline 2012, at clinically relevant concentrations, ceritinib is unlikely to inhibit CYP1A2, 2B6, 2C8, 2C19 or 2D6. Only CYP2A6, 3A4, 2C9 and possibly CYP2E1 need to be considered as possible victims of in vivo inhibition by ceritinib. Ceritinib is also a time-dependent CYP3A inhibitor (Ki: 1.47 μM and Kinact: 0.0642 min^{-1}), but shows no apparent time-dependent inhibition of CYP1A2, 2C9 or 2D6 at ceritinib concentrations of up to 50 μM.

Ceritinib is likely a P-gp, but not BCRP or MRP2 substrate. It does not inhibit P-gp, BCRP or MRP2 at concentrations up to 1.5 μM in vitro.

1.2.1.1.4 Safety pharmacology and toxicology

Ceritinib was evaluated for safety in 2- and 4-week studies in rats and monkeys. The principal toxicity induced by ceritinib was a systemic inflammation characterized by increased neutrophil counts in the peripheral blood and mixed cell/neutrophilic inflammation of the biliopancreatic ducts, pancreas, and/or duodenum. Gastrointestinal toxicity was observed in both species characterized by body weight loss, decreased food consumption, emesis (monkey), diarrhea, and at high doses, by histopathologic lesions including erosion, mucosal inflammation, and foamy macrophages in the duodenal crypts and ampullae of rats and monkeys, respectively. The liver (bile duct) was also affected in both species only at the highest dose levels studied (100 mg/kg/day in the 2-week studies for both rat and monkeys and 50 and 30 mg/kg/day in the 4-week studies in rat and monkeys, respectively), and included increases in liver transaminases in a few animals at high doses, and mixed cell inflammation, erosion and cytoplasmic vacuolation of the bile duct epithelium. The pancreas was a target organ in the rat, but not the monkey, with acinar cell atrophy and mixed cell inflammation noted at middle and high doses. Target organ effects showed partial to complete recovery during the 4-week non-dosing period. No effects in the rat central nervous system or on the respiratory system were observed at single, high doses (100 mg/kg).

[redacted]

Ceritinib has potent activity on the hERG channel with an IC_{50} of 0.4 µM. However, there were no ceritinib -related effects *in vivo* in monkeys at doses as high as 100 mg/kg (human equivalent dose (HED) of 1950 mg).

Preclinical studies (*in vitro* 3T3 NRU assay, refer to [Investigator's Brochure] indicated a low risk of phototoxicity with use of ceritinib. In addition, a preliminary analysis from an *in vivo* ultraviolet local lymph node assay (UV LLNA) demonstrated no phototoxic potential with ceritinib.

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety and tolerability

Ceritinib is associated with a manageable safety profile (Table 1-1). For the 255 patients treated at the recommended dose (RD) of 750 mg in the study [CLDK378X2101], the median duration of exposure as of the 31-Oct-2013 cut-off date was 26.9 weeks (range 0.4 to 82.3 weeks). The most common adverse events (AE) regardless of study drug relationship (incidence ≥25%) were diarrhea, nausea, vomiting, alanine aminotransferase (ALT) increased, fatigue, abdominal pain, decreased appetite, aspartate aminotransferase (AST) increased, and constipation.

The incidence of grade 3-4 AEs, regardless of study drug relationship was <10% for all AEs except ALT increased (26.7%) (Table 1-1). The incidence of grade 3-4 AEs, regardless of study drug relationship was <5% for all AEs except AST increased (8.2%), diarrhea (5.9%), hyperglycemia (5.5%), lipase increased (5.1%), and blood alkaline phosphatase (ALP) increased (5.1%).

[redacted]

Table 1-1 All grades (at least 10%) and associated grade 3-4 adverse events, regardless of study drug relationship, by preferred term in patients treated in the 750 mg dose group (Data cut-off date: 31-Oct-2013)

	Ceritinib 750 mg N=255	
	All Grades	Grade 3/4
Preferred term	n (%)	n (%)
Total	**255 (100.0)**	**184 (72.2)**
Diarrhea	219 (85.9)	15 (5.9)
Nausea	205 (80.4)	11 (4.3)
Vomiting	153 (60.0)	10 (3.9)
Alanine Aminotransferase Increased	110 (43.1)	68 (26.7)
Fatigue	102 (40.0)	10 (3.9)
Abdominal Pain	91 (35.7)	3 (1.2)
Decreased Appetite	87 (34.1)	2 (0.8)
Aspartate Aminotransferase Increased	78 (30.6)	21 (8.2)
Constipation	73 (28.6)	0
Cough	62 (24.3)	0
Abdominal Pain Upper	58 (22.7)	2 (0.8)
Dyspnea	47 (18.4)	8 (3.1)
Asthenia	45 (17.6)	2 (0.8)
Blood Alkaline Phosphatase Increased	45 (17.6)	13 (5.1)
Back Pain	43 (16.9)	1 (0.4)
Headache	41 (16.1)	3 (1.2)
Weight Decreased	39 (15.3)	4 (1.6)
Blood Creatinine Increased	39 (15.3)	0
Pyrexia	38 (14.9)	0
Rash	32 (12.5)	0
Insomnia	31 (12.2)	0
Dyspepsia	26 (10.2)	1 (0.4)
Hypokalemia	26 (10.2)	11 (4.3)
Dizziness	26 (10.2)	0

Dose reductions due to AEs occurred in 58.8% of patients treated with ceritinib at the 750 mg dose; 38.8% of patients had only 1 dose reduction. The most frequent AEs requiring dose adjustments or interruptions reported in ≥5% of the patients were: ALT increased, nausea, AST increased, vomiting, diarrhea, fatigue, and abdominal pain. Adverse events leading to study drug discontinuations occurred in 10.2% of patients treated with ceritinib at the 750 mg dose. The most frequent AEs leading to study drug discontinuations were decreased appetite, pneumonia, ALP, increased, pneumonitis, and respiratory failure.

Serious adverse events (SAEs) reported in 2% or more of the 255 patients treated at the recommended dose of 750 mg were convulsion, pneumonia, interstitial lung disease (ILD)/pneumonitis, dyspnea, hyperglycemia, and nausea. Fatal adverse reactions occurred in

[redacted]

5% of patients, consisting of: pneumonia (4 patients), respiratory failure, ILD/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and sepsis (1 patient each). Adverse events of special interest (AESIs) include hepatotoxicity, ILD /pneumonitis, QT interval prolongation, bradycardia, hyperglycemia gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations), refer to Section 8.1.3 and [Investigator's Brochure].

1.2.1.2.2 Clinical efficacy

As of 31-Oct-2013, data from the [Study CLDK378X2101] demonstrated a high rate of rapid and durable responses with ceritinib in 246 ALK-positive NSCLC patients treated in the 750 mg dose group (RD). In these patients the overall response rate (ORR) was 58.5% (95% CI: 52.1, 64.8) based on investigator assessment (Table 1-2). Among the 144 ALK-positive NSCLC patients with a confirmed complete response (CR) or partial response (PR) based on investigator assessment, 86.1% of those patients achieved a response within 12 weeks, with a median time to response of 6.1 weeks (range: 3.0 to 24.1). The estimated median duration of response (DOR) based on investigator assessment was long at 9.69 months (95% CI: 7.00, 11.40). Based on investigator assessment, the median PFS was 8.21 months (95% CI: 6.70, 10.12) with 53.3% of the patients censored.

Importantly, ceritinib showed this level of high anti-cancer activity regardless of prior ALK inhibitor status(i.e., whether or not the patient received previous treatment with an ALK inhibitor). A high ORR of 54.6% and 66.3% was observed in patients treated with a prior ALK inhibitor and in ALK inhibitor naïve patients, respectively, by investigator assessment (Table 1-2). Rapid responses were observed in patients regardless of prior ALK inhibitor status, 6.1 weeks (range: 4.6 to 24.1) in patients treated with a prior ALK inhibitor and 6.1 weeks (range: 3.0 to 24.1) in ALK inhibitor naïve patients. Further, the estimated median DOR was 7.39 months (95% CI: 5.42, 10.12) in patients treated with a prior ALK inhibitor and the median DOR in the latter group was not reached in ALK inhibitor naïve patients, however the 12-month DOR rate was 65.2% (95% CI: 46.4, 78.8) The estimated median PFS was 6.90 months (95% CI: 5.39, 8.41) in patients treated with a prior ALK inhibitor, while the median PFS was not reached in ALK inhibitor naïve patients (95% CI: 8.31, NE) Finally, ceritinib demonstrated activity in patients with brain metastase at baseline. Among the 98 patients with brain metastasis who had received prior ALK-inhibitor treatment, the ORR was 50% (95% CI: 39.7, 60.3), DOR was 6.9 months (95% CI: 4.8, 8.5), and PFS was 6.7 months (95% CI: 4.9, 8.4). For additional details, refer to [Investigator's Brochure].

[redacted]

Table 1-2 Summary of best overall response based on investigator assessment in NSCLC patients in the 750 mg dose group, by prior ALK inhibitor status (Full Analysis Set NSCLC 750 mg) (Cut-off date: 31-Oct-2013)

	NSCLC with prior ALK inhibitor N=163 n (%)	NSCLC ALK inhibitor naïve N=83 n (%)	All NSCLC N=246 n (%)
Best overall response			
Complete response (CR)	2 (1.2)	1 (1.2)	3 (1.2)
Partial response (PR)	87 (53.4)	54 (65.1)	141 (57.3)
Stable disease (SD)	32 (19.6)	19 (22.9)	51 (20.7)
Progressive disease (PD)	16 (9.8)	0	16 (6.5)
Unknown	26 (16.0)	9 (10.8)	35 (14.2)
Overall response rate (ORR) (CR or PR), n (%)	89 (54.6)	55 (66.3)	144 (58.5)
95% CI	(46.6-62.4)	(55.1-76.3)	(52.1-64.8)

This table presents data for all patients with ALK-positive NSCLC in the 750 mg treatment dose group, **FAS-NSCLC 750 mg group**

Best overall response is based on investigators assessment of disease status using RECIST 1.0 criteria

CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met.

Exact binomial 95% Confidence Interval

1.2.1.2.3 Clinical pharmacodynamics

Data are not available from the ongoing clinical studies.

1.2.1.2.4 Clinical pharmacokinetics

In adult patients with tumors characterized by genetic abnormalities in ALK ([Study CLDK378X2101]) and in healthy subjects ([Studies CLDK378A2101], [Study CLDK378A2104] and [Study CLDK378A2106]), single-dose pharmacokinetics (PK) of ceritinib in humans has the following features: (1) ceritinib was slowly absorbed, with median peak plasma concentration occurring at approximately 4 to 6 h in patients, and approximately 6 to 8 h in healthy subjects. Following Cmax, ceritinib concentrations declined in a mono-exponential manner. The geometric mean apparent terminal half-life ranged from 31 to 41 h across the 400 to 750 mg dose groups in patients and 36 to 48 h across the 450 to 750 mg dose groups in healthy subjects. (2) Cmax and AUC last increased dose-proportionally following single oral administration of ceritinib across the 50 to 750 mg dose groups in patients. (3) moderate to high variability in ceritinib PK parameters has been observed in both healthy subjects and patients. Following single oral doses of 450 to 750 mg in healthy subjects when ceritinib was given alone, the inter-subject variability (geometric mean coefficient of variation; CV% range) was 42-74% and 35-72% for AUClast and Cmax, respectively. The corresponding values in patients were 93% and 87% following single oral doses of 50 to 750 mg based on a model developed for dose proportionality analysis.

[redacted]

Multiple-dose PK of ceritinib following repeated daily oral dosing in patients has the following features: (1) following ceritinib 750 mg once daily dosing, steady-state was reached by approximately 15 days with a geometric mean accumulation ratio (as assessed by AUCtau) of 6.2 after 3 weeks; (2) ceritinib demonstrated nonlinear PK over time, as indicated by the observed difference in apparent clearance (CL/F) between single-dose (88.5 L/h at 750 mg) and steady-state at Cycle 2 Day 1 (33.2 L/h at 750 mg). As ceritinib is a substrate as well as a time-dependent inhibitor of CYP3A, it is likely that this PK nonlinearity could be attributed to auto-inhibition of ceritinib. In contrast with single dose data, Ctrough on Cycle 2 Day 1 after repeated daily dosing increased with dose in a greater than dose-proportional manner.

In the human ADME study [Study CLDK378A2105], the majority of the radioactivity dose in humans was eliminated in the feces (mean: 91.0%) with only a minor amount eliminated in the urine (mean: 1.3%) following a single oral dose of 750 mg of [^{14}C] ceritinib to healthy male subjects. The mean percentage of the dose eliminated in the feces as unchanged ceritinib was 68.0% while all the metabolites were present at low levels, with no individual metabolite contributing greater than 2.3% to the radioactivity AUC. Hepatic metabolism and potentially biliary excretion and GI secretion all contribute to ceritinib elimination in humans while the kidney appears to play a negligible role. The primary biotransformation pathways of ceritinib that were observed included mono-oxygenation, O-dealkylation, and N-formylation. Unchanged ceritinib was the most abundant drug-related component found in both the plasma and excreta.

CYP3A was identified as the major CYP isozyme responsible for the metabolism of ceritinib in humans. An inhibition DDI study conducted in healthy subjects indicated that ketoconazole (200 mg bid for 14 days), a strong CYP3A inhibitor, increased the Cmax and AUCinf of a single 450 mg oral dose of ceritinib by 1.2-fold and 2.9-fold, respectively, compared with ceritinib alone [Study CLDK378A2104]. These results demonstrated that concurrent use of strong CYP3A inhibitors may markedly increase ceritinib exposure and should be avoided. An induction DDI study conducted in healthy subjects indicated that rifampin (600 mg daily for 14 days), a strong CYP3A inducer, decreased the Cmax and AUCinf of a single 750 mg oral dose of ceritinib by 44% and 70%, respectively, compared with ceritinib alone [Study CLDK378A2106]. These results demonstrated that concurrent use of strong CYP3A inducers may markedly decrease ceritinib exposure and should be avoided.

A food effect study was conducted in healthy subjects [Study CLDK378A2101]. Compared to the fasted state, a low-fat meal (approximately 330 calories and 9 grams of fat) increased Cmax and AUCinf of a single oral dose of ceritinib (500 mg) in healthy subjects by 43% and 58%, respectively, whereas a high-fat meal (approximately 1000 calories and 58 grams of fat) increased Cmax and AUCinf by 41% and 73%, respectively.

To further clarify if low fat content has an impact on the extent of ceritinib absorption, a food effect assessment with a very low-fat light snack (containing approximately 100-300 calories and 1.5 grams of fat) was also explored in a relative bioavailability study conducted in healthy subjects [Study CLDK378A2108]. PK data from the light snack cohort showed that when a single 750 mg oral dose of ceritinib was administered with a light snack, the Cmax and AUCinf increased by 45% and 54% respectively, compared to the fasted condition. This magnitude of increase is similar to that caused by a low-fat meal as described in Study

[redacted]

CLDK378A2101, suggesting that even a very low-fat meal could lead to a clinically meaningful LDK378 exposure increase.

Risk and benefits

Overall benefit-risk

Ceritinib dosed at 750 mg once daily has remarkable anti-tumor activity and induces a high rate of rapid and durable responses and prolonged PFS in patients with advanced, ALK-positive NSCLC, regardless of whether they had been previously treated with an ALK inhibitor or were ALK inhibitor naïve. The substantial anti-tumor activity and resulting clinical benefit combined with the clinically manageable safety profile of ceritinib strongly support a positive benefit/risk balance for ALK-positive NSCLC patients.

Efficacy

Patients with prior ALK inhibitor treatment: ALK-positive NSCLC patients previously treated with crizotinib who have progressed and patients intolerant to crizotinib have no effective treatment options, have a dismal prognosis, and represent a population with a high unmet medical need. In ALK-positive NSCLC patients failing treatment with crizotinib, independent from the resistance mechanism involved, ALK translocation is still present and is still the oncogenic driver in almost all of the cases. Chemotherapy is not expected to provide a meaningful clinical benefit in these patients, as was recently demonstrated in a Phase III study (PROFILE 1007) of crizotinib vs. chemotherapy in the second-line setting (Shaw et al 2013).

In ALK-positive NSCLC patients previously treated with an ALK inhibitor and multiple prior lines of anti-neoplastic therapy, based on an independent review of tumor assessments, as of 31-Oct-2013, the response rate was 45.1% (95% CI: 37.1 - 53.3) and the median DOR was 7.1 months (95% CI: 5.6 – NE). The median PFS was 6.7 months (95% CI: 5.5 - 7.7) in Study [CLDK378X2101]. The median PFS is similar (overlapping 95% CIs) to that reported for crizotinib in the second-line setting (7.7 months (95% CI: 6.0 - 8.8)) and similar or better than that reported for chemotherapy (4.2 months (95% CI: 2.8 - 5.7) with pemetrexed and 2.6 months (95% CI: 1.6 - 4.0) with docetaxel) in the PROFILE 1007 study (Shaw et al 2013) for patients with locally advanced or metastatic ALK-positive NSCLC who had received prior treatment with one platinum-containing chemotherapy regimen. Therefore, ceritinib fulfills an existing unmet medical need.

The efficacy of ceritinib seen in Study [CLDK378X2101] is highly encouraging in heavily pretreated patients with advanced disease, high tumor burden (including a high proportion of brain metastases at baseline), limited available therapeutic options, and dismal prognoses following prior ALK-targeted therapies, where the only options are chemotherapy and best supportive care.

ALK inhibitor naïve patients: As of 31-Oct-2013, based on an independent review of tumor assessments, the response rate in ALK inhibitor naïve NSCLC patients was 61.0% (95% CI: 49.2 - 72.0) in Study [CLDK378X2101]. The median DOR was not evaluable for treatment-naïve patients. The median PFS for ceritinib in ALK-inhibitor naïve patients was not evaluable (95% CI: 13.7 - NE) as the majority of patients were ongoing without an event at the time of the data cut-off.

[redacted]

Overall, these data suggest that ceritinib as a first-line ALK inhibitor treatment has remarkable anti-tumor activity and induces a consistently high rate of durable responses in ALK inhibitor naïve patients.

Safety

The safety profile of ceritinib is manageable (Section 1.2.1.2), with a low rate of AEs leading to discontinuation. Furthermore, patients' perception of their quality of life was maintained or slightly improved with ceritinib treatment. The most common AEs were gastrointestinal (diarrhea, nausea, vomiting); increases in transaminases, decreased appetite, fatigue; abdominal pain, and constipation were also seen in ≥ 25% of patients. These AEs can be managed with symptomatic treatment and/or dose reductions or interruptions; only 8.8% of patients discontinued study drug due to an AE. No clinically meaningful differences in the safety profile were observed between ALK-positive NSCLC patients previously treated with an ALK inhibitor and ALK inhibitor naïve patients.

The risks identified with ceritinib treatment include hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia, gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations) (Section 8.1.3). These risks can be managed and ameliorated by early diagnosis and dose adjustment/interruption, or permanent discontinuation.

Risk management during study conduct

In order to manage the risks associated with ceritinib treatment, specific dose modifications and stopping rules during study conduct are described in the protocol. For patients who do not tolerate the initial protocol-specified dose, dose adjustments are provided in order to allow the patients to continue the study treatment (Section 6.3 and Table 6-2). Patients whose treatment is temporarily interrupted or permanently discontinued due to a study drug related AE or an abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

In addition, a thorough post-treatment safety follow-up is included (Section 7.2.4.1). Patients may voluntarily withdraw from study treatment at any time or on the advice of the investigator if he/she believes that continuation would be detrimental to the patient's well-being. When the patient discontinues from study treatment, an End of Treatment (EOT) visit must be performed as soon as possible and within 7 days of the last dose of ceritinib. Patients will also be contacted for the safety follow-up 30 days after their last dose of ceritinib to determine if they have experienced any new AEs and/or to follow resolution of ongoing AEs.

Detailed information on allowed and prohibited concomitant medications is provided in Section 6.3. *In vitro* drug metabolism studies show that the metabolism of ceritinib is mediated by CYP3A4/5. Appendix 1 contains several tables listing medications that are prohibited, permitted or to be used with caution during treatment with ceritinib. Prohibited medications should be discontinued at least 1 week prior to the start of treatment with ceritinib (see exclusion criteria #13).

Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, are extensively described in Section 6.2.8.

[redacted]

Furthermore, regarding adverse events of special interest (see Section 8.1.3):

- Hepatotoxicity: cases of hepatotoxicity occurred in less than 1% of patients treated with ceritinib in clinical studies. Increases to grade 3 or 4 ALT elevations were observed in 25% of patients receiving ceritinib. Concurrent elevations in ALT >3xULN and total bilirubin >2xULN, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical studies. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of ceritinib. Patients will be closely monitored by regular laboratory testing and related signs and symptoms. Risk to patients will also be minimized by restricting study enrollment to subjects with laboratory values for AST, ALT, ALP and bilirubin below certain thresholds (see inclusion criteria #8).
- Interstitial lung disease/pneumonitis: severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been observed in patients treated with ceritinib in clinical studies. Most cases improved or resolved with interruption of ceritinib. Patients will be monitored for symptoms such as shortness of breath, cough or fever. Risk to patients will be minimized by excluding from study enrollment any patient with a history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention) (see exclusion criteria #8).
- QT interval prolongation: QTc prolongation has been observed in clinical studies in patients treated with ceritinib, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death. A pharmacokinetic analysis suggested that ceritinib causes concentration-dependent increases in QTc. Repeated ECG tracings will be performed throughout the study to closely monitor cardiovascular safety. Risk to patients will also be minimized by excluding from study enrollment those patients with clinically significant, uncontrolled heart disease and/or a recent cardiac event (within 6 months), including a corrected QT (QTcF) > 470 ms using Fridericia's correction on the screening ECG (see exclusion criteria #10).
- Bradycardia: asymptomatic cases of bradycardia have been observed in patients treated with ceritinib in clinical studies. Repeated ECG tracings will be performed throughout the study to closely monitor cardiovascular safety. Risk will also be minimized by monitoring concomitant use of other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Heart rate and blood pressure will also be monitored regularly during the study.
- Hyperglycemia: events of hyperglycemia (all grades) have been reported in less than 10% of patients treated with ceritinib in clinical studies; 5% of patients reported a grade 3/4 event. The risk of hyperglycemia was higher in patients with diabetes mellitus and/or concurrent steroid use. Patients will be closely monitored throughout the study for any signs and symptoms related to elevated blood glucose levels. Risk will be minimized by including subjects with fasting plasma glucose levels ≤ 175 mg/dL (≤ 11.1 mmol/L) at screening (see inclusion #8).
- Gastrointestinal toxicity: diarrhea, nausea, and vomiting have been very commonly reported; 12.2% of patients reported a grade 3/4 event of diarrhea, nausea, or vomiting. Risk to patients will be minimized during the study by closely monitoring symptoms and

[redacted]

managing patients using standards of care, including anti-diarrheals, anti-emetics, or fluid replacement, as indicated.

- Pancreatitis (including lipase and amylase elevations): in most cases, pancreatic enzyme elevations have been mild to moderate, and have typically reversed with interruption of ceritinib. Few patients have experienced pancreatitis with severe upper abdominal pain. Patients will be monitored closely for any related signs and symptoms. In order to minimize the risk to patients during the study, patients with a history of pancreatitis or a history of increased lipase or amylase levels that was due to pancreatic disease will be excluded. In addition, serum amylase must be ≤2 x ULN and serum lipase must be within normal limits at screening.

Conclusion

The outstanding anti-tumor activity and resulting clinical benefit combined with the manageable safety profile of ceritinib strongly support a positive benefit-risk balance for ALK-positive NSCLC patients, regardless of whether the patients had received prior ALK inhibitor treatment or not.

The risk to subjects in this trial will be minimized and managed by compliance with the eligibility criteria, close clinical monitoring, dose modifications/interruptions and permanent discontinuation as required. There may be unforeseen risks with LDK378 which could be serious. Refer to the [Investigator's Brochure] for additional information regarding the safety profile of ceritinib.

2 Rationale

2.1 Study rationale and purpose

2.1.1 Rationale for the use of ceritinib in ALK-driven tumors

Ceritinib is a novel inhibitor of ALK that in preclinical studies is more potent and specific than crizotinib, and is active in a broad range of ALK-activated tumor models, including models driven by mutated versions of ALK known to be resistant to crizotinib, and by ALK gene amplification.

As described in Section 1.1, genetic alterations of ALK are found in subsets of several cancers. Both *in vitro* and *in vivo* experiments have demonstrated that neuroblastoma, ALCL, and NSCLC models carrying ALK alterations are frequently dependent on ALK for their growth, and are responsive to treatment with ALK inhibitors (Chiarle 2003, Soda 2007, Li 2011, Galkin 2007). Butrynski et al (2010) reported sustained partial response to the ALK inhibitor (PF-02341066, crizotinib) in ALK+ IMT patient, whereas no observed activity was found in another patient without ALK translocation. The small study suggests potential therapeutic benefit for genetically identified patients with aggressive and life threatening tumors with limited treatment options while Mosse et al (2012) demonstrated that the ALK inhibitor (PF-02341066, crizotinib) has antitumor activity in children with neuroblastoma and ALCL. Bang et al (2010) demonstrated that use of an ALK inhibitor (PF-02341066, crizotinib) in heavily pretreated EML4-ALK expressing non-small cell lung cancer patients

[redacted]

resulted in a response rate of >60%. The responses were durable and the safety profile of the drug was deemed acceptable. Shaw et al (2014) demonstrated that ALK inhibitor (LDK378, ceritinib) was highly active in patients with advanced, ALK-rearranged NSCLC, including those who had had disease progression during crizotinib treatment.

Together, these preclinical and clinical data support evaluation of ceritinib in patients with malignancies carrying genetic alterations of ALK. It is therefore reasonable to formulate a hypothesis that predefined diverse populations of patients suffering from life threatening tumors such as ALCL, IMT, GBM, IBC as well as any other tumor associated with ALK dysregulation may be effectively treated with ceritinib.

2.2 Rationale for the study design

This is a phase II, open-label, multicenter, parallel multi-arm, clinical trial that will be assessing ceritinib as monotherapy in diverse populations of patients with various life threatening tumors other than NSCLC. Given the variety of diseases to be treated, the study design is exploratory in nature and tumor types have been selected based on the scientific rationale of the presence of ALK dysregulation. Antitumor activity of ceritinib in any tumor type will be evaluated in a non-comparative single arm to support the POC that inhibition of dysregulated ALK activity might prove to be an important antineoplastic intervention for the targeted diseases.

The selected tumors in this study are considered rare based on the low prevalence of the ALK dysregulation as recorded in the published literature. Depending on the tumor type, patients will be enrolled into one of 5 parallel arms:(Arm 1) ALCL; (Arm 2) IMT; (Arm 3) GBM; (Arm 4) Inflammatory Breast Cancer and (Arm 5) Any other ALK+ tumor. If there 5 or more patients of the same tumor type in the “Any other ALK+ tumor” arm, then a separate arm will be opened for that specific tumor type. Only patients whose tumors harbor ALK genetic alteration (and/or overexpression in some diseases) will be enrolled in the study.

Patients must have received at least one line of prior systemic therapy for recurrent, locally advanced and/or metastatic disease and must not be candidates for any alternative therapy. They may have progressed or may be intolerant to standard therapy. There will be no reference control arm. The study will initially enroll 10 patients in each arm: ALCL; GBM and Any other ALK+ tumor. The IMT arm will enroll 5 patients due to the rare incidence of this tumor type.

Interim analysis for an arm will be performed when a predefined number of patients (5 for IMT and 10 for all other tumor type) have completed 16 weeks of treatment with ceritinib and have their anti-tumor activity assessed. Responses observed at week 16 (CR or PR) must be confirmed by a subsequent assessment at least 4 weeks later. An additional 10 patients may be enrolled for a given arm (including IMT) subsequent to the interim analysis if the probability of the pre-defined clinically meaningful response for the arm is at least 20%.

Bayesian hierarchical model (BHM) to estimate the DCR for each arm and its 95% credible interval and posterior probability of being clinically meaningful will be applied. The proposed model is a modified version of standard model (Thall 2003, Chugh 2009) which assumes full exchangeability (similarity) between the disease-specific response rates. The total number of patients to be enrolled per arm will be based on an adaptive design. The adaptive design will

[redacted]

be patient-sparing and allow the early closure of non-responding arms and continuation of enrollment of arms which show meaningful clinical activity. Approximately 106 patients 18 years and older are planned to be enrolled. Patients must be diagnosed with a life threatening malignancy that have a genetic alteration of ALK (such as a mutation, translocation amplification, and/or overexpression in some diseases) and have progressed or are intolerant following standard therapy.

2.3 Rationale for dose and regimen selection

In the global phase I study CLDK378X2101, where a majority of the patients were diagnosed with NSCLC, the MTD and recommended dose for the adult patients 18 years and older for the expansion cohorts and future trials was determined to be 750 mg daily (QD).

The dose escalation phase of the phase I study CLDK378X2101 was completed in May 2012 (Shaw et al 2014). Fifty-nine patients were treated at the following dose levels: 50 mg (2 patients), 100 mg (2 patients), 200 mg (3 patients), 300 mg (3 patients), 400 mg (14 patients), 500 mg (10 patients), 600 mg (10 patients), 700 mg (5 patients), and 750 mg (10 patients). DLTs were observed in 6 patients:

- 400 mg: hypophosphatemia and ALT elevation (1 patient each)
- 600 mg: diarrhea and dehydration (1 patient each)
- 750 mg: diarrhea/vomiting (1 patient) and diarrhea/nausea (1 patient)

Ceritinib 750 mg dose once daily oral is the approved dose and will be used in this study.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

3 Objectives and endpoints

This is an efficacy POC study to determine the preliminary anti-tumor activity and safety and tolerability of ceritinib in advanced ALK+ solid tumors (other than NSCLC) and ALK+ hematologic malignancies.

Primary objective:

To assess the antitumor activity of ceritinib treatment as measured by Disease Control Rate (DCR) based on local investigator assessment.

Antitumor activity in each arm will be evaluated after 16 weeks of ceritinib treatment and will include responses of CR or PR or SD. The primary end point DCR at 16 weeks since the start of the treatment is considered clinically meaningful duration of drug activity in the selected patient population.

For patients with solid tumors the assessment criteria will be RECIST 1.1. For GBM, RANO and RECIST 1.1 criteria will apply. For hematologic tumors, Cheson response criteria will

[redacted]

apply. DCR will include complete response (CR), partial response (PR) or stable disease (SD) at 16 weeks since the start of the treatment. The responses will need to be confirmed at least 4 weeks later by the same method.

Secondary objectives:

- To assess the antitumor activity of ceritinib as measured by ORR, DOR, TTR determined by investigators
- To assess the antitumor activity of ceritinib as measured by PFS determined by investigators
- To assess safety and tolerability:
  Hematology, biochemistry, urinalysis, coagulation, pregnancy test and hormones (males only); ECG; Performance status; Physical examination, Vital signs; Adverse events CTCAE 4.03 will be used to assess events.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
To assess the antitumor activity of ceritinib as measured by DCR determined by investigators	DCR, defined as the proportion of patients with best overall response of CR, PR, or SD ≥ 16 weeks of ceritinib treatment	
Secondary		Refer to Section 10.5.1.
1. To assess the antitumor activity of ceritinib as measured by ORR determined by investigators	1. ORR, defined as the proportion of patients with a best overall response defined as CR or PR; (CR+PR)	
2. To assess the antitumor activity of ceritinib as measured by DOR,TTR and PFS determined by investigators	2. The following endpoints will be evaluated by investigator assessment per RECIST 1.1, RANO and Cheson criteria: a. DOR, defined as the time from date of first documented CR or PR to date of first documented disease progression or death due to any cause b. TTR, defined as the time from date of the first dose to date of first documented response (CR or PR) c. PFS, defined as time from date of the first dose to date of first documented disease progression (assessed by investigators per RECIST 1.1) or date of death due to any cause For GBM, RANO and RECIST 1.1 criteria will apply. For hematologic tumors, Cheson response criteria will apply.	
3. To assess the safety profile of ceritinib	3. ECG, Performance status, Vital signs, Physical examination; AEs (assessed by CTCAE 4.03), and laboratory (hematology, biochemistry, urinalysis, coagulation, pregnancy test and hormones (males only),	

Objective	Endpoint	Analysis
[redacted]		

4 Study design

4.1 Description of study design

This is a Phase II, open-label, multicenter, parallel multi-arm, POC clinical trial that will assess anti-tumor activity and safety and tolerability of ceritinib as monotherapy in patients with life threatening locally advanced or metastatic solid tumors other than NSCLC and hematological malignancies (see Table 4-1) characterized by ALK genetic alteration (and/or overexpression in some diseases).

Patients must have received at least one prior systemic, anti-cancer therapy for locally advanced and/or metastatic disease. In addition, patients may have had prior surgery and/or radiotherapy and/or adjuvant and/or neoadjuvant systemic therapy. ALCL patients may have had a prior autologous stem cell transplant (ASCT). There will be at least 4 different tumor types in parallel arms in adult patients:

Table 4-1 Tumor types of interest

	Tumor Types of interest
1.	Anaplastic Large Cell Lymphoma (ALCL)
2.	Inflammatory Myofibroblastic Tumor (IMT)
3.	Glioblastoma (GBM)
4.	Inflammatory Breast cancer (IBC)
5.	Any other ALK+ tumor

Locally documented ALK genetic alteration (and/or overexpression in some diseases) determined for specific tumor types as by the protocol defined ALK genetic alteration (and/or overexpression in some diseases) (see Table 4-2) is acceptable. All patients are required to have a pathology report, including the ALK test results, and an archival or fresh tumor tissue sample available prior to the first dose of the study treatment for potential retrospective confirmation of ALK positivity by a Novartis designated central laboratory if deemed necessary. The results from the ALK test report must be entered into the eCRF prior to the first dose of the study treatment.

The confirmation of ALK positivity by the Novartis designated central laboratory is not required for enrollment if other inclusion and exclusion criteria are fulfilled Novartis will conduct the confirmatory retrospective ALK test if, and at the time considered necessary. The tumor samples will be kept in the storage until a decision will be made to perform a confirmatory test; at that time selected samples will be shipped to the central laboratory. The confirmatory ALK test will be performed before the end of the study. Acceptable archival tumor tissue may consist of a formalin fixed paraffin embedded (FFPE) tumor block (preferred) or at least 5, or more slides 4-5 µm thick. The minimum number of slides is indicated in order to have sufficient material for ALK determination. If a tumor block is provided, the remaining tissue will be returned to the site upon request.

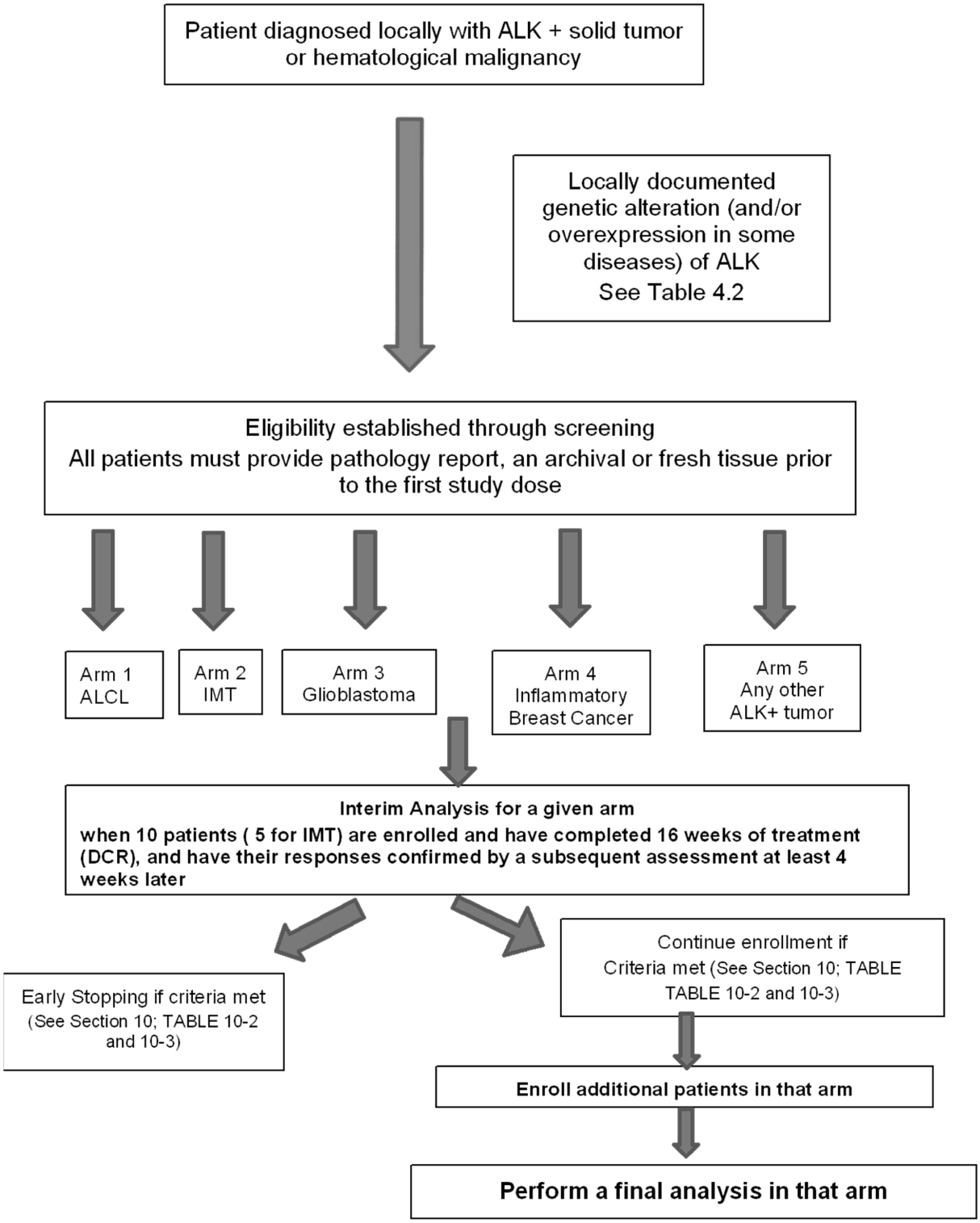
Table 4-2 Locally documented generic alterations of ALK are accepted

Tumor type	Genetic Alteration of ALK		
	Translocation involving ALK Gene	ALK Protein over expression	Mutation, amplification involving ALK Gene*, **
Anaplastic Large Cell Lymphoma (ALK+)	√	√	√
Inflammatory Myofibroblastic Tumor	√	-	-
Inflammatory breast cancer	√	-	√
Glioblastoma	√	√	√
Any other ALK + tumor	√	-	√

* An amplification of the ALK gene, defined as ≥ 6 copies per cell, or 3 copies per haploid genome. When assessed by FISH, ALK amplification must be observed in focal clusters of tumor cells (not only single cells) or in more than one-third of the tumor cells.

**A known activating mutation in the kinase domain of ALK or a point mutation in the kinase domain of ALK that results in an amino acid change that has not been reported in normal germline DNA, or any other mutation (e.g. insertion or deletion) which results in a change in the amino acid sequence of the kinase domain of ALK, as long as the alteration does not clearly result in inactivation of the kinase activity, such as deletion of the kinase domain, or a stop codon preventing translation of the kinase domain.

Figure 4-1 Study design



4.1.1 Duration of treatment

Patients will continue ceritinib until they experience any of the following:

- Disease progression (radiologically documented according to RECIST 1.1, RANO and RECIST 1.1 for GBM or by Cheson criteria for hematologic malignancies).
- Unacceptable toxicity that precludes further treatment
- Start of a new anti-cancer therapy
- Pregnancy
- Treatment is discontinued at the discretion of the investigator or patient
- Lost to follow-up
- Death
- Study terminated by Sponsor

Patients treated with ceritinib who have RECIST, RANO or Cheson -defined progressive disease but who, in the opinion of the investigator, have evidence of continuing clinical benefit from ceritinib may continue to receive this drug. In such cases, patients must complete the EOT visit only after permanent discontinuation of ceritinib.

4.1.2 End of treatment (EOT)

Patients will continue to receive study treatment until disease progression (assessed by investigator per RECIST 1.1 for solid tumors, RANO and RECIST 1.1 criteria for GBM or Cheson criteria for ALCL), unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator), otherwise known as End of Treatment. All patients who discontinue from study treatment due to disease progression must have their progression clearly documented.

4.2 Timing of interim analyses and design adaptations

Interim analysis for each arm will be performed for decision making (early stopping or continuation of recruitment) when a predefined number of patients (5 for IMT and 10 for all other arms) have completed 16 weeks of treatment with ceritinib and have their anti-tumor activity assessed. Responses observed at week 16 (CR or PR) must be confirmed by a subsequent assessment at least 4 weeks later. The reduced number of patients (5) in the IMT arm is based on the rare incidence of this tumor type. An additional 10 patients may be enrolled for a given arm (including IMT) subsequent to the interim analysis if the probability of the pre-defined clinically meaningful response for the arm is at least 20%.

All available data will be used for analysis at the interim. For a specific arm, a decision will be made based on the calculated probability as given below:

- If the posterior probability of being clinically meaningful (Table 10-1) is less then 20% then recruitment will be stopped in that arm
- Otherwise, recruitment will be extended for 10 more patients in that arm

All available data will be used for analysis at the interim. However, a decision will be made only for arms with a minimum number of pre-specified patients (a minimum of 5 patients in

[redacted]

IMT arm or a minimum of 10 patients for any of the other arm). Depending on enrollment and follow-up, there may be multiple interim analyses. Details of the interim analysis is given in Section 10.7.

4.3 End of the study

The study will end approximately 38 weeks after the last patient started treatment with study medication or once at least 75% of patients have died or have been lost to follow-up or withdraws consent, or when the study is terminated early. The primary analysis for a given arm will occur once all patients in that arm complete at least 16 weeks of treatment with ceritinib unless discontinued earlier; have their efficacy evaluation completed at week 16 and the responses are confirmed by subsequent visit within 4 weeks and EOT visit completed 30 days later. The final analysis of study data will be conducted at the end of the study

Novartis may continue to supply ceritinib to patients who may benefit from continued treatment as per the Investigator's opinion. Novartis will make every effort to provide study medication for patients who continue to experience benefit from the treatment.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible for an end of treatment (EOT) visit and the assessments for EOT should be performed as described in Section 7 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board (IRB) and/or Ethics Committee (EC) of the early termination of the trial.

5 Population

5.1 Patient population

This study will be conducted in previously treated male or female patients 18 years and older. Approximately 106 patients are planned to be enrolled to have 95 evaluable patients. Patients must be diagnosed with one of the per protocol selected ALK+ life threatening malignancy that has a dysregulation of ALK (such as a mutation, translocation, amplification or overexpression) (see Section 4.1 Table 4-2). In addition, patients must have progressed following at least one line of prior systemic treatment for recurrent, locally advanced and or metastatic disease or are intolerant to therapy.

The investigator or designee must ensure that only patients who meet all of the inclusion and none of the exclusion criteria are offered treatment in the study. All tumor specific arms will enroll patients in parallel. The patient must not receive any additional anti-cancer therapy during treatment with ceritinib.

Written informed consent must be obtained prior to any screening procedures.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies while on treatment. Rescreening may be allowed up to 2

[redacted]

times; laboratory parameters and ECGs may be retested within the 28-day screening period for an individual patient if such parameters meet an exclusion criterion when initially tested.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Written informed consent for the main study obtained prior to any screening procedure.
2. Patient must have a histologically or cytologically confirmed diagnosis of one of the tumors that is ALK positive (ALK+). The ALK test results must be available at the investigator site before the first dose of the study drug. The tumor types are described below:

Anaplastic Large Cell Lymphoma (ALCL), local confirmation of diagnosis of ALK+ ALCL is sufficient for eligibility.

Inflammatory Myofibroblastic Tumor locally documented translocation involving the ALK gene,

Glioblastoma, Inflammatory breast cancer Any other locally documented ALK+ tumor must carry a locally documented genetic alteration of ALK including any of the following (ALK overexpression is also acceptable in Gliobalstoma):

- A known activating mutation in the kinase domain of ALK or a point mutation in the kinase domain of ALK that results in an amino acid change that has not been reported in normal germline DNA, or any other mutation (e.g. insertion or deletion) which results in a change in the amino acid sequence of the kinase domain of ALK, as long as the alteration does not clearly result in inactivation of the kinase activity, such as deletion of the kinase domain, or a stop codon preventing translation of the kinase domain.
- An amplification of the ALK gene, defined as ≥ 6 copies per cell, or 3 copies per haploid genome. When assessed by FISH, ALK amplification must be observed in focal clusters of tumor cells (not only single cells) or in more than one-third of the tumor cells.
- A translocation involving the ALK gene.
- Glioblastoma patients only, an overexpression of the ALK protein (documented locally is also acceptable for eligibility).

3. Patient must provide an archival or fresh tumor tissue before the first dose of the study drug for potential retrospective ALK testing at a Novartis designated central laboratory by a comparative technology:
   - the confirmation of ALK positivity is not required for enrollment if other inclusion and exclusion criteria are fulfilled.
4. Patient is 18 years or older at the time of informed consent.
5. Patient has WHO performance status ≤ 2.
6. Patient must have received at least one line of prior systemic treatment for recurrent, locally advanced and/or metastatic disease, may have discontinued for:
   - Disease progression: defined by RECIST 1.1 for solid tumors; by RANO for GBM and by Cheson assessment criteria for lymphoma

[redacted]

- Intolerance, described as any discontinuation due to an AE of any grade despite appropriate supportive treatment

7. Patient must have a wash-out period prior to the first dose of ceritinib:
   - Chemotherapy, immunotherapy, stem cell transplant within 4 weeks
   - Radiotherapy and ALK inhibitors must have discontinued within 1 week
   - Recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v4.03). Exception to this criterion: patients with any grade of alopecia are allowed to enter the study.
8. Patient must have at least one measurable lesion as defined by appropriate guidelines. A lesion at a previously irradiated site may only be counted as a target lesion if there is clear sign of progression since the irradiation.
   - Solid Tumors: by RECIST 1.1 (Section 14.2)
   - GBM: by RANO and RECIST 1.1 (Section 14.3 and Section 14.2)
   - ALCL: by Cheson (Section 14.4). Patient has at least one measurable nodal lesion (≥1.5 cm). In case where the patient has no measurable nodal lesions ≥ 1.5 cm in the long axis at screening, then the patient must have at least one measurable extra-nodal lesion.
9. Patient must meet the following laboratory values at the screening visit:
   - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L;
   - Platelets ≥ 75 x 10^9/L)
   - Hemoglobin ≥ 8 g/dL
   - International Normalized Ratio (INR) ≤ 1.5
   - Serum creatinine ≤ 1.5 mg/dL and/or calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 30 mL/min;
   - Total bilirubin ≤ 1.5 x upper limit of normal (ULN), except for patients with Gilbert's syndrome, who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN;
   - Aspartate transaminase (or aminotransferase; AST) ≤ 2.5 x ULN, except for patients with liver metastasis, who are only included if AST ≤ 5 x ULN;
   - Alanine transaminase (or aminotransferase; ALT) ≤ 2.5 x ULN, except for patients with liver metastasis, who are only included if AST ≤ 5 x ULN;
   - Alkaline phosphatase (ALP) ≤ 5.0 x ULN.
   - Serum amylase ≤ 2 x ULN
   - Serum lipase ≤ ULN
   - Fasting plasma glucose≤175 mg/DL (≤9.8 mmol/L)
10. Patient must have the following laboratory values within ≤ Gr1 (CTCAE v4.03) at screening:
    - Potassium
    - Magnesium
    - Phosphorus

[redacted]

- Total calcium (corrected for serum albumin)

11. Patient must be willing and able to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patient with ALK+ lung cancer.
2. Patient with known hypersensitivity to any of the excipients of LDK378 (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate).
3. Patient with symptomatic CNS metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms.
4. History of carcinomatous meningitis,
5. Patient with diarrhea CTCAE ≥ grade 2; or patients with neuropathy CTCAE ≥ grade 2
6. Patients with acute or chronic GI disease that may significantly alter the absorption of ceritinib
7. Patient with a history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease
8. Patient has history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis
9. Presence or history of a malignant disease other than primary tumor under consideration that has been diagnosed and/or required therapy within the past 3 years.
    - Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
10. Patient has clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months) such as:
    - unstable angina within 6 months prior to screening;
    - myocardial infarction within 6 months prior to screening;
    - history of documented congestive heart failure (New York Heart Association functional classification III-IV);
    - uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication
    - initiation or adjustment of antihypertensive medication(s) is allowed prior to screening;
    - ventricular and atrial arrhythmias; supraventricular and nodal arrhythmias not controlled with medication;
    - Other cardiac arrhythmia not controlled with medication.
    - Corrected QT (QTcF) >470 ms using Fridericia's correction on the screening ECG (as mean of triplicate ECGs).

11. Evidence of active viral hepatitis, including Hepatitis A, B or C (testing for viral hepatitis is not mandatory).
12. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory).
13. Patient receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with ceritinib and for the duration of the study:
    - Strong inhibitors or strong inducers of CYP3A4/5
    - Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5 and/or CYP2C9
    - Medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes
14. Patients who are currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants.
15. Patient receiving unstable or increasing doses of corticosteroids.
    If patient is on corticosteroids for endocrine deficiencies or tumor-associated symptoms (non-CNS), dose must have been stabilized (or decreasing) for at least 5 days before first dose of study treatment.
16. Patient receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of study treatment, and for the duration of the study. Patients on non-enzyme-inducing anticonvulsants are eligible.
17. Major surgery (e.g., intrathoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting study treatment or who have not recovered from side effects of such procedures.
18. Pregnant or nursing (lactating) women
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and for 3 months after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
        - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

[redacted]

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

20. Sexually active male unless they use a condom during intercourse while taking the drug and for 3 months after the last dose of LDK378 treatment. Male patients should not father a child for 3 months after the last dose of LDK378 treatment. For male patients treated with reference chemotherapy they should not father a child for at least 6 months after the last dose of treatment or as per the local label. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
21. Patient has other severe, acute, or chronic medical or psychiatric conditions including uncontrolled diabetes mellitus or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results.

6 Treatment

6.1 Study treatment

For this study, the term “investigational treatment” refers to ceritinib (LDK378).

The ceritinib dose and treatment schedule of the study treatments are listed in Table 6-1. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.1.1 Dosing regimen

A complete treatment cycle is defined as 28 days of once daily continuous treatment with ceritinib. The first dose of study treatment defines Day 1 of the treatment cycle and the last day of a complete treatment cycle is Day 28. Those patients without confirmed Progressive Disease (i.e., those with CR, PR, SD,) will continue receiving treatment with ceritinib until disease progression, unacceptable toxicity or withdrawal from the study for other reasons.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Ceritinib	Hard gelatin capsule for oral use	750 mg (5 x 150 mg capsule	Once daily (28 day cycle)

6.1.2 Ceritinib administration

Each study site will be supplied with ceritinib by Novartis. Ceritinib is supplied as individual patient supply, packaged in bottles. Medication labels for the globally provided study treatment ceritinib will comply with legal regulations of each country and be printed in local language. The storage conditions for the study treatment will be described on the medication label.

- Patients will self-administer ceritinib on an outpatient basis. The investigator must instruct the patient to take the study drug exactly as prescribed. Patients should take ceritinib once

[redacted]

daily at approximately the same time each day, in the morning, afternoon, or at the bed time.

- [redacted]
- Patients should take ceritinib on an empty stomach (i.e. fast from food and drink, except water) at least 2 hour before or 2 hours after a light meal.
- Each dose of ceritinib should be taken with a glass of water and consumed over as short a time as possible (i.e. not slower than 1 capsule every 2 minutes).
- Patients should be instructed to swallow whole capsules and not to chew or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

Patients must be instructed not to make up missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 8 hours after the approximate time of the usual daily dosing. That day's dose (or part remaining dose) should be omitted and the patient should continue treatment with the next scheduled dose on the following day.

6.1.3 Ancillary treatments

Not applicable.

6.1.4 Rescue medication

Not applicable.

6.2 Dose escalation guidelines

Not applicable.

6.2.1 Starting dose rationale

Not applicable.

6.2.2 Provisional dose levels

Not applicable.

6.2.3 Guidelines for dose escalation and determination and dose delay

Not applicable.

[redacted]

6.2.4 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patients to continue the study treatment. Any changes in ceritinib administration must be recorded on the Dosage Administration Record eCRF.

Detailed ceritinib dose modification guidelines for selected toxicities are described in Section 6.2.5 and Table 6-2. All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 4.03).

General guidelines for dose modifications for toxicities other than those listed in Table 6-2:

For grade 1 and tolerable grade 2 treatment-related toxicities, patients are encouraged to continue at the current dose of study treatment. For intolerable grade 2 treatment-related toxicities, dosing should be interrupted until resolution to grade 1 or lower followed by dose reduction to the next dose level.

For grade 3 or grade 4 treatment-related toxicity that is not considered by the investigator to be life-threatening, patients should interrupt study treatment until resolution to grade 1 or lower; then study treatment may continue following a dose reduction to the next dose level, if, in the opinion of the Investigator, the patient continues to experience clinical benefit. For any grade 3 or 4 treatment-related toxicity that is considered by the investigator to be life-threatening, permanently discontinue study treatment.

6.2.5 Treatment interruption and treatment discontinuation

If the administration of ceritinib is temporarily interrupted for reasons other than toxicity then treatment with ceritinib will be resumed at the same dose.

If treatment with ceritinib is withheld due to toxicity, scheduled visits and all assessments will continue to be performed (with the exception of the dosing of the withheld study drug), as described in Table 7-1.

If treatment with ceritinib is withheld for more than 28 consecutive days (counting from the first day when a dose was missed) due to treatment-related toxicity, then ceritinib should be permanently discontinued except in cases where the investigator believes the patient continues to derive clinical benefit. In such cases, treatment with ceritinib may be resumed at a lower dose.

Patients whose treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event. Detailed guidelines for follow-up of study drug related AEs or abnormal laboratory values must be followed as described in Section 6.2.6.

All patients will be followed for safety until 30 days after the last dose of ceritinib.

6.2.6 Criteria for ceritinib dose modifications

A ceritinib dose reduction will follow the guidelines described in Table 6-1. For each patient, a maximum of 3 dose reductions will be allowed. All dose reductions will be in 150 mg decrements per reduction. The patient must be discontinued from treatment with ceritinib if further reduction is necessary. Once the dose of ceritinib has been reduced due to toxicity, it cannot be re-escalated.

Table 6-2 Dose reduction steps for ceritinib

Ceritinib dose levels	Dose* and schedule
Starting dose level	750 mg qd
Dose level – 1	600 mg qd
Dose level – 2	450 mg qd
Dose level – 3	300 mg qd **

*Dose reduction should be based on the worst preceding toxicity

**Dose reduction below 300 mg/day is not allowed. If a dose reduction below 300 mg/day is required, the patient should be permanently discontinued from ceritinib

Guidelines for dose modification and dose interruption of ceritinib are described in Table 6-2.

[redacted]

Table 6-3 Criteria for interruption and re-initiation of ceritinib treatment

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for ceritinib**
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC <1.5 and ≥1.0 x 10^9/L) Grade 3 (ANC <1.0 and ≥0.5 x 10^9/L)	Maintain dose level Maintain dose level If resolved to ≤ Grade 2, then ↓ 1 dose level
Grade 4 (ANC <0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤7 days, then maintain dose level If resolved in >7 days, then ↓ 1 dose level
Febrile neutropenia (ANC <1.0 x 10^9/L, with a **single** temperature of ≥38.3 °C or a sustained temperature of ≥38 °C for more than one hour)	Omit dose until clinically resolved and neutropenia ≤ Grade 2, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT <75 and ≥50 x 10^9/L)	Maintain dose level
Grade 3 (PLT <50 and ≥25 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤7 days, then maintain dose level If resolved in >7 days, then ↓ 1 dose level
Grade 4 (PLT <25 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level
HEPATIC	
Alkaline phosphatase and/or Gamma-glutamyl transpeptidase (GGT)	
Isolated elevations of any grade	Maintain dose level
Total Bilirubin** (for patients with Gilbert Syndrome these dose modifications apply to changes in direct [conjugated] bilirubin only)	
Grade 1 (> ULN and ≤1.5 x ULN)	Maintain dose level with liver function test (LFTs)*** monitored as per protocol

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for ceritinib**
Grade 2 (>1.5 and ≤3.0 x ULN) with AST or ALT ≤3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤7 days, then maintain dose level If resolved in >7 days, then ↓ 1 dose level
Grade 3 (>3.0 and ≤10.0 x ULN) with AST or ALT ≤3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤7 days, ↓ 1 dose level If resolved in >7 days discontinue patient from ceritinib
Grade 4 (>10.0 x ULN)	Permanently discontinue patient from ceritinib
AST or ALT	
Grade 1 (> ULN and ≤3.0 x ULN)	Maintain dose level with LFTs*** monitored per protocol
Grade 2 (>3.0 and ≤5.0 x ULN) without total bilirubin elevation to >2.0 x ULN	Maintain dose level with LFTs*** monitored per protocol
Grade 3 (>5.0 and ≤20.0 x ULN) without total bilirubin elevation to >2.0 x ULN	Omit dose until resolved to ≤ Grade 1 (or to baseline), then ↓ 1 dose level
Grade 4 (>20.0 x ULN) without total bilirubin elevation to >2.0 x ULN	Omit dose until resolved to ≤ Grade 1 (or to baseline), then ↓ 1 dose level
AST or ALT and concurrent Total bilirubin	
AST or ALT >3.0 x ULN and total bilirubin >2.0 x ULN in the absence of cholestasis or hemolysis	Permanently discontinue patient from ceritinib. Refer to Section 6.2.7.2 for additional follow-up
PANCREATIC	
Amylase and/or lipase elevations (in the absence of clinical symptoms)	
Grade 1 (> ULN and ≤1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 - 2.0 x ULN)	Maintain dose level
Grade ≥3 (> 2.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Note: Withhold ceritinib for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for ceritinib**
RENAL	
Serum creatinine	
Grade 1 (>1 and ≤1.5 x baseline; > ULN and ≤1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 and ≤3.0 x baseline; >1.5 and ≤3.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤7 days, then maintain dose level If resolved in >7 days, then ↓ 1 dose level
Grade 3 (>3.0 x baseline; >3.0 and ≤6.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (>6.0 x ULN)	Permanently discontinue patient from ceritinib
GASTROINTESTINAL	
Diarrhea**	
Grade 1	Maintain dose level but adjust anti-diarrhea treatment
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then maintain dose level. If diarrhea returns as ≥ Grade 2, then omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 3 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Nausea***	
Grade 1 or 2	Maintain dose level but adjust anti-emetic treatment
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Vomiting***	
Grade 1	Maintain dose level but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then maintain dose level. If vomiting returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then ↓ 1 dose level.
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for ceritinib**
METABOLIC	
Any Grade **hypophosphatemia**	Treatment with phosphate supplements as clinically indicated and maintain dose level
Persistent **hyperglycemia** (glucose >250 mg/dL) despite optimal anti-hyperglycemic therapy	Omit dose until hyperglycemia is adequately controlled, then resume ceritinib at ↓ 1 dose level If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue patient from ceritinib.
GENERAL DISORDERS	
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	If grade 3 fatigue resolves to Grade 2 in ≤7 days, maintain dose level If grade 3 fatigue lasts >7 days, omit dose until resolved to ≤ Grade 2 and then ↓ dose level
PULMONARY	
Notes: • Withhold ceritinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD. • During evaluation of potential grade 2, 3, and 4 pneumonitis, if an infectious etiology is confirmed (i.e., pneumonia) and pneumonitis is excluded, and then consider resuming ceritinib at current dose level after the pneumonia resolves.	
PNEUMONITIS	
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue patient from ceritinib
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTc 450-480 ms) Grade 2 (QTc 481-500 ms)	Maintain dose level

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for ceritinib**
Grade 3 (QTc ≥501 ms on at least two separate ECGs)	Omit dose until QTc is less than < 481ms, then ↓ 1 dose level • Assess the quality of the ECG recording and the QT value and repeat if needed Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTc < 481 ms In addition:-Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment • Review concomitant medication use for drugs with the potential to increase the risk of drug exposure related to QT prolongation • Consider collecting a time-matched [redacted] sample and record time and date of last study drug intake After resumption of dosing: • Repeat ECGs 7 days after dose resumption for all patients who had therapy interrupted due to QTc ≥ 501 ms.
Grade 4 (QTc ≥501 or >60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue patient from ceritinib
Bradycardia	
Grade 1 or 2	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥60 bpm Evaluate concomitant medications known to cause bradycardia, and adjust the dose of ceritinib.
Grade 3 Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥60 bpm If the concomitant medication can be adjusted or discontinued, resume ceritinib at ↓ 1 dose level with frequent monitoring
Grade 4 (in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension)	Permanently discontinue ceritinib.

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	Dose Modifications for ceritinib
* Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All dose modifications should be based on the worst preceding toxicity. ** If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the Investigator. ***LFTs include albumin, ALT, AST, total bilirubin, alkaline phosphatase and GGT **** Dose modifications apply to patients who experience diarrhea despite appropriate antidiarrheal medication. This medication should be started at the first sign of abdominal cramping, loose stools or overt diarrhea (see Section 6.2.7.6) ***** Dose modifications apply to patients who experience nausea and/or vomiting despite appropriate antiemetic medication. This medication should be started at the first sign of nausea and/or vomiting (see Section 6.2.7.5)	

[redacted]

6.2.7 Follow-up for toxicities

An unscheduled visit should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments (Table 7-1).

6.2.7.1 Guidelines for the follow-up of laboratory hematologic abnormalities

In case of any occurrence of febrile neutropenia, neutropenia ≥ grade 3, or thrombocytopenia ≥ grade 3, tests must be performed weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 2. Subsequent monitoring must be performed every 4 weeks. See Table 6-3.

6.2.7.2 Guidelines for the follow-up of laboratory liver abnormalities

In patients with any clinically relevant laboratory liver abnormality, as defined below, hepatic toxicity monitoring must include ALL of the following liver function tests (LFTs): albumin, AST, ALT, total bilirubin (fractionated if total bilirubin >2.0 x ULN), alkaline phosphatase and GGT). Note: for patients with Gilbert Syndrome, total and direct bilirubin must be monitored, but intensified monitoring applies to changes in direct bilirubin only.

In case of any occurrence of AST/ALT/total bilirubin increase to grade 2, the LFTs must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Thereafter monitoring must be continued every other week (or more frequently if clinically indicated) for two additional cycles (e.g. 8 weeks). If there is no recurrence of grade 2 AST/ALT/total bilirubin elevations during this period, subsequent monitoring must be performed every 4 weeks. For patients with liver metastasis and grade 2 AST/ALT at baseline, increased monitoring is required for grade 3/4 AST/ALT; follow guidelines for grade 3 or 4 AST/ALT.

In case of any occurrence of AST/ALT/total bilirubin increase to grade 3 or 4, LFTs must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 (or to baseline). Thereafter monitoring must be continued every other week (or more frequently if clinically indicated) for four additional cycles (e.g. 16 weeks). If there is no recurrence of ≥ grade 2 AST/ALT/total bilirubin elevations during this period, subsequent monitoring must be performed every 4 weeks.

Patients who discontinue study treatment due to liver toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 4 weeks). Refer to Table 6-4.

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient’ s baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT or AST or TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN

[redacted]

- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: ALP elevation > 2.0 x ULN with R value (ALT/ALP in x ULN) < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatinine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (eg, biliary tract) may be warranted.
- [redacted]
- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant”, thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented.

6.2.7.3 Guidelines for the follow-up of laboratory renal abnormalities

In case of any occurrence of serum creatinine grade ≥2, tests must be performed weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Subsequent monitoring must be performed every 4 weeks.

In case of any occurrence of serum creatinine ≥ grade 3, tests must be performed twice weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Subsequent monitoring must be performed every 4 weeks. Refer to Table 6-3.

[redacted]

6.2.7.4 Guidelines for monitoring pneumonitis

Monitor patients for pulmonary symptoms indicative of pneumonitis. In addition, withhold ceritinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD.

See also dose modification guidelines described in Table 6-2.

6.2.7.5 Guidelines for the treatment of study drug induced nausea and vomiting

Nausea and vomiting are among the most frequently reported AEs following treatment with ceritinib and patients must therefore be closely monitored for the appearance of these AEs.

The investigator should consider/investigate potential concomitant medication, food or comorbidity-driven causes of nausea and/or vomiting and remedy these causes if possible (e.g., discontinuation of concomitant medication, dietary modification, treatment of comorbidity).

Individualized supportive and anti-emetic treatment should be initiated, as appropriate, at the first signs and/or symptoms of these AEs. In patients with vomiting, the patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration.

Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator's best judgment. For moderate emetogenic drugs, such as ceritinib, International Guidelines for anti-emetic treatment recommend early treatment with 5-HT3-receptor antagonists (5-HT3RAs).

Dose adaptation of ceritinib in case of treatment related nausea and/or vomiting must follow the guidelines presented above in Table 6-2.

6.2.7.6 Guidelines for the treatment of study drug induced diarrhea

The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g., discontinuation of concomitant medication, dietary modification, treatment of comorbidity).

The patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practice and the investigator's best judgment and may follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004). For example:

- For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at a standard dose (e.g., initial administration of 4 mg, then 2 mg every 2-4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures should be considered. Note: complicating signs or symptoms include: moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration.

[redacted]

- For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms), management should involve intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg SC tid or 25 to 50 µg IV) and antibiotics (e.g. fluoroquinolone) should be given.

Dose adaptation of ceritinib in case of treatment related diarrhea must follow the guidelines presented above in Table 6-2.

6.2.7.7 Guidelines for treatment of hypophosphatemia

In the phase I study [CLDK378X2101], as of 31-Oct-2013, there were 9 cases of grade 3 hypophosphatemia in all dose groups, one of which was a DLT that contributed to the MTD determination – this patient was able to continue ceritinib at the same dose. One patient in the 750 mg group had grade 3 hypophosphatemia that resolved after dose adjustment or interruption; in the remaining 8 cases, patients were able to continue therapy without dose modification. Hypophosphatemia was a commonly reported AE (6.3%), regardless of relationship to ceritinib treatment. Therefore, phosphate levels will be checked at baseline and during treatment. In cases of hypophosphatemia at baseline, phosphate supplements should be started before treatment withceritinib. For any grade of hypophosphatemia during the study, treatment with phosphate supplements should be given as clinically indicated, and the ceritinib dose can be maintained.

6.2.7.8 Guidelines for the follow-up of laboratory pancreatic abnormalities

In case of any occurrence of lipase or amylase increase to grade 3 or 4, both lipase and amylase must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 (or to baseline).

After resumption of dosing, monitoring must be continued weekly (or more frequently if clinically indicated) for one additional cycle (i.e. 4 weeks). If there is no recurrence of ≥ grade 2 amylase or lipase elevations during this period, subsequent monitoring must be performed every 4 weeks.

Patients who discontinue study treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 3 weeks). Refer to Table 6-3.

If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, withhold ceritinib, then perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.

See also dose modification guidelines in Table 6-2.

[redacted]

Table 6-4 Follow-up evaluations for selected toxicities

Toxicity	Follow-up evaluation*
Investigations (hematologic)	**Febrile neutropenia, neutropenia or thrombocytopenia ≥ CTCAE Grade 3** Test weekly (or more frequent) until ≤ Grade 2 Subsequent monitoring must be performed every cycle (4 weeks)
Investigations (hepatic)	**Total bilirubin/AST/ALT Grade 2:** (patients with liver metastasis and grade 2 AST/ALT at baseline, increased monitoring required for grade 3 ALT/AST. Follow guidelines for grade 3 or 4 AST/ALT Test weekly (or more frequently) until ≤ Grade 1 Thereafter, continue to test every 2 weeks (or more frequently) for 2 cycles (8 weeks) If no recurrence of ≥ Grade 2 event, continue monitoring every cycle (4 weeks) **Total bilirubin/ALT/AST ≥ Grade 3:** Test weekly (or more frequent) until ≤ Grade 1 Thereafter, continue to test every 2 weeks (or more frequently) for 4 cycles (16 weeks) If no recurrence of ≥ grade 2 event, continue monitoring every cycle (4 weeks) **Discontinuation due to liver toxicity:** Test weekly (or more frequent) until ≤ Grade 1 or stabilization
Investigations (renal)	**Serum creatinine Grade 2:** Test weekly (or more frequent) until Grade 1 Thereafter, test every cycle (4 weeks) **Serum creatinine ≥ Grade 3:** Test twice weekly (or more frequent) until ≤ Grade 1 Thereafter, test every cycle (4 weeks)
Investigations (pancreatic)	**Amylase/lipase ≥ Grade 3:** Test weekly (or more frequently) until ≤ Grade 1. After resumption of dosing, continue to test weekly for one additional cycle (4 weeks). If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle (4 weeks).

*Note: this table refers to the evaluation schedule only. Refer to Table 6-2 for dose modifications required for applicable toxicities

6.2.8 Anticipated risks and safety concerns of the study treatment

Appropriate eligibility criteria and specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, e.g., diarrhea are provided in Section 6.2.4. Refer to preclinical toxicity and or clinical data found in the IB.

6.3 Concomitant medications

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient (e.g., anti-emetics, anti-diarrheal) is permitted (see Section 6.3.1), except when specifically prohibited (see Section 6.3.2).

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications including herbal/natural medications (excluding study treatment and prior antineoplastic treatments and blood transfusions),

[redacted]

surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose of administration of ceritinib through 30 days after the last dose of ceritinib will be recorded in the Concomitant Medications or Surgical and Medical Procedures eCRF, respectively. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications (prohibited, see Section 6.3.2.7), food and or vitamin supplements.

6.3.1 Permitted concomitant therapy

6.3.1.1 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to induce CYP3A enzymes, thereby increasing the risk of reducing ceritinib drug exposure to sub-therapeutic levels.

If possible, systemic corticosteroid treatment should not be given during the study, except for:

- Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular);
- Stable doses of corticosteroid therapy such as dexamethasone and prednisone (e.g., for tumor associated symptoms) are permitted during the course of the study. The corticosteroid dose must have been stabilized (or decreasing) for at least 5 days before initiating study therapy.

6.3.1.2 Bisphosphonates

The use of bisphosphonates is allowed regardless of indication provided patients have been on stable doses optimally for at least 4 weeks prior to the start of treatment. Patients requiring initiation of bisphosphonate treatment during the course of the study should be discontinued due to progressive disease and the result of the evaluation should be clearly documented in the patients' source documentation.

No drug-drug interaction is expected between ceritinib and bisphosphonates as the two drugs are eliminated through different elimination pathways. Bisphosphonates are not inhibitors of human CYP450 enzymes involved in the metabolism of ceritinib and do not undergo metabolism *in vivo*.

The same guidelines apply to the use of denosumab for the treatment of bone metastatic disease.

6.3.1.3 Drugs that are metabolized by CYP450 enzymes

In vitro drug metabolism studies show that the metabolism of ceritinib is mediated by CYP3A4/5. Ceritinib is a time-dependent CYP3A4/5 inhibitor and is also a potent reversible inhibitor of CYP2A6, 2E1, 2C9 and 3A4/5 and may consequently increase exposure to drugs metabolized by these enzymes at clinically relevant concentrations. Clinical studies have not yet been performed to confirm the potential effect of ceritinib on substrate drugs metabolized by these enzymes in patients. The risk for CYP2A6 and CYP2E1 is largely mitigated by the low potential for drugs metabolized by these enzymes to be co-administered with ceritinib.

[redacted]

Concomitant treatment of ceritinib with weak inhibitors or inducers of CYP3A4/5 is permitted. Caution is advised when ceritinib is co-administered with drugs that are moderate inhibitors or inducers of CYP3A4/5 (Appendix 1, Table 14-2). Duration of concomitant treatment should be kept as short as possible (e.g., less than 1 week), or completely avoided whenever possible. Patients receiving such medications must be monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and may require dose titration or adjustment. Note that co-administration of ceritinib with strong inhibitors or inducers of CYP3A4/5 is prohibited (refer to Section 6.3.2.5).

Concomitant treatment of ceritinib with medications known to be metabolized by CYP2C9 and CYP3A4 is allowed with caution (Appendix 1, Table 14-2), except for drugs which have narrow therapeutic index/sensitive substrates for these CYP isoforms (Appendix 1, Table 14-1).

6.3.1.4 Non-enzyme inducing anti-epileptic drugs

Non-enzyme inducing anti-epileptic medication (Non-EIAED) is allowed.

6.3.1.5 Palliative radiotherapy and surgery

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. If a target bone lesion requires palliative radiotherapy, the patient should be discontinued from the study. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be assessed and documented.

Patients who develop progressive disease but are still deriving clinical benefit from ceritinib therapy, as determined by the Investigator may undergo radiotherapy and/or surgical resection as palliative localized therapy to treat metastatic lesions. Ceritinib should be held for at least 4 days prior to radiotherapy and at least 1 day prior to any surgery. Ceritinib may be resumed ≥3 days after completing radiotherapy or minor surgery, and ≥2 weeks after major surgery.

6.3.1.6 Gastric protection agents

The use of gastric protection agents including antacids, H2-antagonists, and proton pump inhibitors (PPIs) is allowed (Appendix 1). However, PPIs should be used with caution due to the theoretical effects of long-acting pH elevating agents (i.e., prolonged acid suppression) on reducing ceritinib absorption. When the concurrent use of a H2-antagonist or an antacid with ceritinib is necessary, the H2 blocker must be administered 10 hours before or 2 hours after the ceritinib dose, and the antacid must be administered 2 hours before or 2 hours after the ceritinib dose. Time restrictions for the concurrent use of PPIs and ceritinib are not applicable due to the long-acting effects of PPIs on gastric pH (i.e., separation of doses will not likely impact this interaction).

6.3.2 Prohibited concomitant therapy

6.3.2.1 Other anticancer therapy

Anticancer therapy (chemotherapy, targeted therapy, biologic therapy or radiation therapy [except palliative radiotherapy and palliative surgery as described in Section 6.3.1.5], and anti-cancer surgery), other than the study treatment, must not be given to patients while they are enrolled in the treatment portion of the trial. If such agents are required then the patient must be permanently discontinued from the treatment portion of the study.

6.3.2.2 Other investigational therapies

Other investigational therapies must not be used while the patient is on the study.

6.3.2.3 Warfarin and coumarin derivatives

Therapeutic doses of warfarin sodium or any other coumarin-derivative anticoagulants are not permitted. Ceritinib is an inhibitor of CYP2C9, the major metabolizing enzyme of warfarin. A clinically relevant increase in warfarin exposure is possible.

6.3.2.4 Enzyme inducing anti-epileptic drug

Use of EIAEDs is not permitted. Refer to Appendix 1, Table 14-3 for a list of prohibited EIAED.

If a patient is currently taking an EIAED, he/she must have discontinued the EIAED therapy for at least 1 week prior to starting study drug.

If a patient was previously on a non-EIAED and needs to permanently change anticonvulsant agent but cannot change to another non-EIAED, the patient will be taken off ceritinib.

6.3.2.5 Strong CYP3A inhibitors and inducers

In vitro metabolism studies suggest that oxidative metabolism of ceritinib is predominantly mediated by CYP3A4/5.

Strong inhibitors or inducers of CYP3A4/5 are prohibited. Patients receiving concomitant medications known to strongly inhibit and/or induce CYP3A4/5 that are deemed medically necessary should be excluded from the study. Refer to Appendix 1, Table 14-1 for a list of these medications. Please note that this list may not be comprehensive.

6.3.2.6 Medications that are CYP2C9 and CYP3A4/5 substrates with narrow therapeutic index

Ceritinib is a potent inhibitor of drugs metabolized by CYP2C9 and CYP3A4/5 *in vitro*. Because of the potential risk for drug-drug interactions, using medications known to be metabolized by these enzymes and that have a narrow therapeutic index is not permitted concomitantly with ceritinib. Refer to Appendix 14-1, Table 14-1 for a list of these medications. Please note that this list may not be comprehensive.

[redacted]

6.3.2.7 Herbal medications

Herbal preparations/medications are not allowed throughout the study, as a potential drug-drug interaction is always possible. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

Patients should stop using herbal medications at least 7 days prior to first dose of study treatment.

6.3.2.8 Medications that may prolong the QT interval or have a known risk of inducing Torsades de Pointes

Ceritinib has potent activity on the hERG channel with an IC_{50} of 0.4 μM. There were no ceritinib-related effects *in vivo* in monkeys at doses as high as 100 mg/kg (human equivalent dose [HED] of 1950 mg).

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in an open-label, dose-escalation, and expansion [Study CLDK378X2101]. A total of 304 patients were treated with ceritinib doses ranging from 50 to 750 mg with 255 patients treated with ceritinib 750 mg. One of 304 patients (<1%) was found to have a QTc >500 msec and 10 patients (3.3%) had an increase from baseline QTc >60 msec. A central tendency analysis of the QTc data at average steady-state concentrations demonstrated that the upper bound of the 2-sided 90% CI for QTc was 16 msec at ceritinib 750 mg. A pharmacokinetic/pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation

Concomitant use of ceritinib and any medication included in Appendix 14-1, Table 14-4 titled "List of prohibited QT prolonging drugs" (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a known risk of causing Torsades de Pointes) is not permitted.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first screened and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each Patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available at the site.

6.4.2 Treatment assignment

The Investigator or his/her delegate will contact the IRT and confirm that the patient fulfills all the inclusion and exclusion criteria. The IRT will assign a number to the patient, which will be used to link the patient to the treatment and will specify unique medication numbers for the first packages of study treatment to be dispensed to the patient.

[redacted]

IRT must be notified within 2 days in case that the patient did not start treatment.

6.4.3 Treatment blinding

Not applicable.

6.5 Study drug preparation and dispensation

6.5.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Study treatment labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

Table 6-5 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Ceritinib	150 mg capsules in HDPE bottles	Labeled as LDK378 (daily)

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

Table 6-6 Supply and storage of study treatments

Study treatments	Supply	Storage
Ceritinib	Centrally supplied by Novartis	Refer to study treatment label

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

[redacted]

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation.

All data obtained from these assessments must be supported in the patient’s source documentation. No eCRF will be used as a source document. The table indicates which assessments produce data to be entered into the database (D) or remain in the source documents (S) only.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening Day-28 to -1	Treatment Phase							Safety Follow-up
				Cycle 1		Cycle 2		Cycle 3	Subsequent Cycles CxD1 (±3 day)	End of study Treatment (EoT)	
Visit Name			Screening	C1D1	C1D15 (±1 day)	C2D1 (±3 day)	C2D15 (±3 day)	C3D1 (±3 day)	CxD1 (±3 day)		
Obtain Informed Consent	D	7.2.1.	X								
Tumor sample (archival or fresh) for ALK testing for patients (obtained prior to first dose)	D	7.3.4.	X								
Documentation of local ALK testing results (ALK amplification, ALK mutation, ALK translocation, and/ or ALK protein overexpression)	S/D		X								
Demography	D	7.2.1.2.	X								
Inclusion/exclusion criteria	S/D	5.2 & 5.3.	X								
Eligibility checklist	S		X								
End of phase disposition	D		X							X	
Tumor type identification (ALK+ solid or hematological tumor type)	D	4.1.	X								
Relevant medical history/ current medical conditions	D	7.2.1.2.	X								
History of smoking	D	7.2.1.2.	X								
Diagnosis and Extent of cancer	D	7.2.1.2.	X								
Prior anti-neoplastic therapy	D	7.2.1.2.	X								

[redacted]

	Category	Protocol Section	Screening Day-28 to -1	Treatment Phase							Safety Follow-up
				Cycle 1		Cycle 2		Cycle 3	Subsequent Cycles CxD1 (±3 day)	End of study Treatment (EoT)	
Visit Name			Screening	C1D1	C1D15 (±1 day)	C2D1 (±3 day)	C2D15 (±3 day)	C3D1 (±3 day)	CxD1 (±3 day)		
Prior and concomitant medications	D	7.2.1.2.	X	Continuous							
Surgical and medical procedures	D	7.2.1.2.	X	Continuous							
Physical examination	S	7.3.2.1.	X	X		X		X	X	X	
WHO performance status	D	7.3.2.4.	X	X		X		X	X	X	
Vital signs	D	7.3.2.2.	X	X	X	X	X	X	X	X	
Height	D	7.3.2.3.	X								
Weight	D	7.3.2.3.	X	X		X		X	X	X	
ECG	D	7.3.2.6.	X	X	X	X	X	X		X	
Ceritinib administration	D	6.1.2.		Daily							
[redacted]											
Hematology	D	7.3.2.5.1.	X	X	X	X	X	X	X	X	
Biochemistry (including liver function tests, lipase and amylase)	D	7.3.2.5.2.	X	X	X	X	X	X	X	X	
Testosterone, LH, FSH, sex hormone binding globulin (SHBG)	D	7.3.2.5.3.	X	X	X						
Coagulation	D	7.3.2.5.6.	X	X							
Urinalysis (dipstick)	D	7.3.2.5.3.	X	X	X	X	X	X	X	X	
Pregnancy test	D	7.3.2.5.4.	X	X		X		X	X	X	
Adverse events	D	8.1.1.	X	X	Continuous						X

[redacted]

	Category	Protocol Section	Screening Day-28 to -1	Treatment Phase							Safety Follow-up
				Cycle 1		Cycle 2		Cycle 3	Subsequent Cycles CxD1 (±3 day)	End of study Treatment (EoT)	
Visit Name			Screening	C1D1	C1D15 (±1 day)	C2D1 (±3 day)	C2D15 (±3 day)	C3D1 (±3 day)	CxD1 (±3 day)		
TUMOR EVALUATION											
Physical examination for measurement of superficial disease (only if present)	S	7.3.1.	X	Every 8 weeks after first dose of study drug (Day 1 of every odd cycle)						X	
Examination for enlarged spleen or liver for lymphoma	S	7.3.1.	X	To confirm CR						X	
Radiological tumor assessment/ response assessment (MRI/CT/PET-CT Scans) (± 7 days)	D	7.3.1.	X	Every 8 weeks (±7 days) from C1D1 to C6D1. Every 12 weeks (±7 days) after C6D1						X (if not performed within 8 weeks since the last assessment)	
Bone Marrow bilateral aspirate or Biopsy (±7 days) for lymphoma (if applicable at screening)	D	7.3.1.	X	To confirm CR						X (if positive at screening)	

[redacted]

7.2 Molecular pre-screening

Not Applicable

7.2.1 Screening

Written informed consent must be obtained before any study specific assessments are performed, including screening. All screening evaluations (see Table 7-1) must be performed as closely as possible to the beginning of treatment (within 28 days of the start of ceritinib) to confirm patient's eligibility.

Patients must be diagnosed with one of the per protocol selected ALK+ malignancy that has a dysregulation of ALK (such as a mutation, translocation, amplification or overexpression) (see Section 4.1 Table 4-2). The results of this testing must be known prior to signing the ICF and before formal screening begins. Patient must have archival tissue available for submission to allow for future confirmatory ALK testing. If the tissue is not available or not of sufficient quantity, the patient must be willing to undergo a fresh tumor biopsy to allow for this analysis. The tumor sample (archival or fresh) submitted will not be used to determine study eligibility.

Rescreening may be allowed up to 2 times; laboratory parameters and ECGs may be retested within the 28-day screening period for an individual patient if such parameters meet an exclusion criterion when initially tested. If the repeated result meets the criterion, that result may be used to determine eligibility. If the repeated laboratory parameters and ECG results do not meet the criterion, the patient will be considered a screening failure.

Patients will undergo baseline radiological assessments as detailed in Section 7.3 and Table 7-2.

7.2.1.1 Information to be collected on screening failures

A patient who signs the informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure. The reason for not satisfying eligibility criteria and not being enrolled in the study will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion eCRF pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). If the patient fails to be enrolled, the IRT must be notified within 2 days of the screen fail that the patient was not enrolled.

The following eCRFs must be completed for screening failure patients:

- Screening Phase Disposition page
- Informed consent
- Demography
- Adverse Events (only if an SAE occurs. Refer to Section 8.1.1.)
- Inclusion/Exclusion Criteria

[redacted]

7.2.1.2 Patient demographics and other baseline characteristics

Data to be collected on patient characteristics at screening include:

- Demography (including: date of birth, age, gender, childbearing potential, race and ethnicity or as allowed by local regulations)
- Relevant medical history
- Smoking history
- Tumor diagnosis and extent of disease, including:
- Date of diagnosis and tumor stage at diagnosis
- Site of active disease
- Characteristics of disease
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and Concomitant Medications, surgical and medical procedures

Note: All other medications taken within 28 days before the first dose of study treatment is administered must be recorded on the Prior and Concomitant medication eCRF page and updated on a continual basis if there is new change to the medication.

7.2.2 Treatment period

Following completion of screening procedures and verifying patient eligibility, the patient will be enrolled via the IRT. Study treatment will begin on Cycle 1, Day 1 with the first administration of ceritinib. Cycle 1, Day 1 must occur within 28 days of screening date.

7.2.2.1 General guidelines

Patients will be assessed as per visit schedule in Table 7-1.

Visit windows of ± 1 days for Cycle 1 and ± 3 days for Cycle 2 and beyond from the scheduled study assessments will apply in all cycles. The only exception is imaging assessments, which have a ± 7 day window at all scheduled time points. If a given visit is out of window, the next visit should be performed with reference to the day of first dose in order to get the patient back on schedule.

Patients will begin treatment on Day 1. Patients will self-administer study treatment at home daily.

Note: If treatment with ceritinib is withheld at any time during the study, all study visits, safety and efficacy assessments should continue according to the appropriate number of calendar days from Cycle 1 Day 1 as per the schedule of assessments.

[redacted]

7.2.3 End of treatment (EOT) visit including study treatment discontinuation and premature withdrawal

7.2.3.1 Study treatment discontinuation

Patients may voluntarily withdraw from study treatment at any time. In this situation, the patient should be encouraged to consent to be followed for tumor assessments until the development of Progressive Disease as assessed by the investigator.

Patients must permanently stop the study treatment if one of the following occurs:

- Pregnancy
- Study Terminated by Sponsor
- Patient/guardian decision
- Physician decision
- Lost to follow-up
- Death

Patients may permanently stop the study treatment for one of the following reasons:

- Progression of disease (for example radiological as assessed by investigators for solid tumors)
- AEs
- Non-compliance with study treatment
- Technical Problems
- Protocol deviation

Patients who become pregnant during the trial must be withdrawn (Section 8.4). Patients who become pregnant must cease all tumor assessments regardless of whether or not they developed Progressive Disease.

Patients who discontinue ceritinib during the treatment phase should be scheduled for a visit within 7 days or as soon as possible after the last dose of study treatment, at which time all of the assessments listed for the EOT visit will be performed. If a patient withdraws from treatment at a study visit, EOT assessments do not need to be repeated. An End of Treatment Phase Disposition eCRF page should be completed, specifying the date of the subject's last participation in the treatment study phase and reason for stopping study treatment.

Patients who have RECIST, RANO or Cheson defined Progressive Disease, but who, in the opinion of the investigator, have evidence of continued clinical benefit from ceritinib may continue to receive this drug. These patients will continue assessments as detailed in Table 7-1 treatment phase except for the tumor assessments. In such cases, patients must complete the EOT visit only after permanent discontinuation of ceritinib.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them. Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

[redacted]

7.2.3.1.1 Additional guidance for premature withdrawal

If a patient will have no further study data collected because he/she withdraws from the study completely, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the EOT Disposition eCRF as applicable. The investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Patients may voluntarily withdraw from the study or be discontinued from the study at the discretion of the investigator at any time. The Investigator must contact the IRT to register the subject's discontinuation.

7.2.3.2 Replacement policy

Patients lost to follow-up or withdrawing consent from the study without observed response rate will be censored for the primary analysis and will not be replaced.

7.2.4 Follow up period

7.2.4.1 Safety follow-up

All patients will be followed for AEs and SAEs for at least 30 days following the last dose of study treatment at the end of treatment phase. At the end of this period, the investigator should assess and discuss with the patient any AE observed/concomitant medication taken since discontinuation of study treatment.

Patients whose treatment is permanently discontinued due to an AE (clinical or based on abnormal laboratory value) must be followed until resolution or stabilization of the event, whichever comes first. In case of an abnormal laboratory value, blood tests should be repeated until resolution or stabilization.

7.2.4.2 Lost to follow-up

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.3 Assessment types

7.3.1 Efficacy assessments

Tumor response will be assessed by the investigator according to the Novartis guideline version 3.1 based on RECIST 1.1 (Eisenhauer et al 2009) for solid tumors; The Revised Assessment in Neuro-Oncology (RANO) and RECIST 1.1 criteria for Glioblastoma (Wen et al 2010) and Response Criteria for Malignant Lymphoma (Cheson et al 2007). Patients should have at least one documented measurable lesion at study entry as per RECIST 1.1.; RANO and Cheson criteria. The imaging assessment collection plan is presented in Table 7-2.

[redacted]

At screening (within 28 days of the start of ceritinib), patients will undergo CT with i.v. contrast or MRI or PET-CT (lymphoma patients). If there is clinical evidence of disease in the neck, a CT or MRI of the neck will also be performed. If a patient is intolerant of iodine-based contrast agents, CTs may be performed without contrast or MRI may be used. If there is clinical evidence of disease in the bone marrow at screening, bone marrow aspirate biopsies must be performed (for ALCL patients only).

Disease evaluations after the screening assessment will include evaluation of all sites of disease identified at baseline, using the same technique that was used at screening. If there was no evidence of disease in a body region at baseline, that region does not need to be imaged at subsequent assessments, unless there is clinical concern for a new lesion in that body region

Table 7-2 Imaging assessment collection plan

Procedure	Screening/Baseline	During Treatment/ EOT
CT or MRI or PET-CT of Chest, Pelvis and Abdomen	Mandated For GBM patients: If there is clinical evidence of disease	Mandated, every 8 weeks (± 7 days) from C1D1 to C6D1. For subsequent sycles, every 12 weeks (± 7 days) after C6D1. For the EOT, only to be performed if the last assessment was more than 8 weeks.
Brain CT or MRI	Mandated	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen
Whole body bone scan	Only if clinically indicated	If clinically indicated
• CT scan or MRI of other metastatic sites (e.g., neck etc.) • Localized bone CT scan, MRI or x-ray (for any lesions identified on the whole body bone scan that are not visible on the chest/abdomen (and pelvis if applicable) CT scan or MRI)	Only if clinically indicated	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen

7.3.1.1 Baseline imaging assessment

Imaging assessments will be performed at screening/baseline Day -28 to Day -1 prior to Cycle 1 Day 1. Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study.

The following assessments are required at screening/baseline:

- CT scan or MRI or PET-CT (lymphoma patients) of chest, pelvis and abdomen. For GBM patients only if there is clinical evidence of disease.
- CT scan or MRI of brain

The following assessments are required at screening if clinically indicated:

[redacted]

- Additional CT scan or MRI of other metastatic sites (e.g., neck,etc.)
- Localized bone CT scan, MRI or x-ray (for any lesions identified on whole body bone scan not visible on chest/abdomen (and pelvis if applicable) CT scan or MRI)
- Whole body bone scan

If a patient is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis (as applicable) should be performed.

Brain, MRI or CT scan should be completed in order to assess CNS disease. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then brain MRI without contrast or brain CT with/without contrast is acceptable.

A whole body bone scan should be performed per institutional standard of care if clinically indicated to detect any skeletal metastases present [e.g., Tc-99 bone scan, whole body bone MRI, FDGPETor sodium fluoride positron emission tomography (NaF PET)]. Localized CT, MRI or Xrays should be acquired for all skeletal lesions identified on the screening bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI.

If clinically indicated, CT or MRI of other areas (neck,etc) of disease as appropriate should be performed.

Required conditions for baseline tumor assessment:

- Patients must have measurable disease as per RECIST 1.1, RANO and Cheson.
  Measurable ("target") lesions include lytic or mixed (lytic + blastic) bone lesions with an identifiable soft tissue component that meets the measurability criteria per RECIST 1.1.
- Patients with only non-measurable lesions are not eligible.
  If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable ("non-target") lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

All measurable lesions up to a maximum of 5 nodal and/or non-nodal lesions in total (and a maximum of 2 lesions per organ), representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.

7.3.1.2 Subsequent imaging for response assessment

Tumor evaluations as described in Table 7-2 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1). Tumor assessment for response determination will be made every 8 weeks starting from C1D1 (+/- 7 days window) until C6D1. For subsequent cycles, every 12 weeks (+/- 7 days window) ater C6D1. Scheduled assessments should be respected regardless of whether treatment with ceritinib is temporarily withheld.

[redacted]

Clinical suspicion of disease progression at any time requires a physical examination and radiological confirmation to be performed promptly rather than waiting for the next scheduled radiological assessment.

Each lesion that is measured at baseline must be measured by the same method (either same radiological method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule. Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and IV contrast media.

If an off-schedule scan is performed for response confirmation purposes, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

7.3.2 Safety and tolerability assessments

Safety will be monitored by assessing **(list the assessments)** as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.3.2.1 Physical examination

Physical examinations will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a basic nervous system evaluation. Information about the physical examination must be present in the source documentation at the study center. For the assessment schedule refer to Table 7-1.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.3.2.2 Vital signs

Vital signs include body temperature, blood pressure, respiratory rate and pulse measurements. Blood pressure (systolic and diastolic) and pulse should be measured after the patient has been sitting for five minutes.

For the assessment schedule refer to Table 7-1.

7.3.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at screening only. For the assessment schedule for weight refer to Table 7-1.

7.3.2.4 Performance status

Performance status may be performed within 3 days prior to the start of a cycle.

WHO performance status will be assessed as per the assessment schedule (refer to Table 7-1) in adult patients 18 years and older.

Assessment of WHO performance status (Table 7-3) will be performed within the time windows described of the scheduled assessment, even if study treatment is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 7-3 WHO performance status scale

Score	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.3.2.5 Laboratory evaluations

Central laboratories will be used for the analysis of scheduled biochemistry and ALK confirmatory testing (as detailed in Table 7-1). Hematology tests will be performed locally. Dipstick urinalysis will be performed locally. Laboratory values obtained during the Screening phase will be used to assess patient's eligibility. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 7.1).

Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in a separate [Laboratory Manual].

[redacted]

Table 7-4 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Red blood cells (RBC), White blood cells (WBC) with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils in percentage or absolute)
Chemistry	Albumin, ALT, AST, calcium (at screening calcium corrected for albumin will be tested in addition to calcium), creatinine, creatinine clearance, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, fasting glucose, phosphate (inorganic phosphorus), alkaline phosphatase, amylase, lipase, GGT
Urinalysis	Macroscopic Panel (Dipstick) (Color, bilirubin, Blood, Glucose, Ketones, Leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)
Coagulation	International normalized ratio [INR]
Pregnancy	At screening visit, serum pregnancy test At subsequent cycles, urinary pregnancy test. If local requirements dictate otherwise, local regulations should be followed
Hormones (males only)	Testosterone (total and free), LH, FSH, sex hormone binding globulin (SHBG)

7.3.2.5.1 Hematology

Hematology assessments of the parameters listed in Table 7-4 will be tested as per the schedule of assessments (Table 7-1).

7.3.2.5.2 Clinical chemistry

Blood chemistry assessments of the parameters listed in Table 7-4 will be tested as per the schedule of assessments (Table 7-1).

7.3.2.5.3 Urinalysis

Dipstick measurements will be performed as per Table 7-4 and according to the schedule of assessments. Any significant findings on dipstick will be followed up with microscopic evaluation as per Table 7-4.

7.3.2.5.4 Pregnancy and assessments of fertility

During screening, a serum pregnancy test will be completed (Day -28 to Day -1). On cycle 1 Day 1 prior to dosing and at subsequent cycles and at EOT, urinary pregnancy test (dipstick) will be performed. The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit. Refer to Table 7-1. If local requirements dictate otherwise, local regulations should be followed.

When non-child bearing potential status is determined during the study, further pregnancy testing will not be continued. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal

[redacted]

ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential (such testing is not covered as part of the study assessments). If local requirements dictate otherwise, local regulations should be followed.

The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit. Refer to Table 7-1.

If a positive pregnancy test is performed in between study visits, the patients must immediately notify the investigator.

7.3.2.5.5 Hormones

Testosterone (total and free), LH, FSH and SHBG will be tested in male patients only and as per the schedule of assessments (Table 7-1).

7.3.2.5.6 Coagulation

International normalized ratio (INR)

7.3.2.6 Cardiac assessments

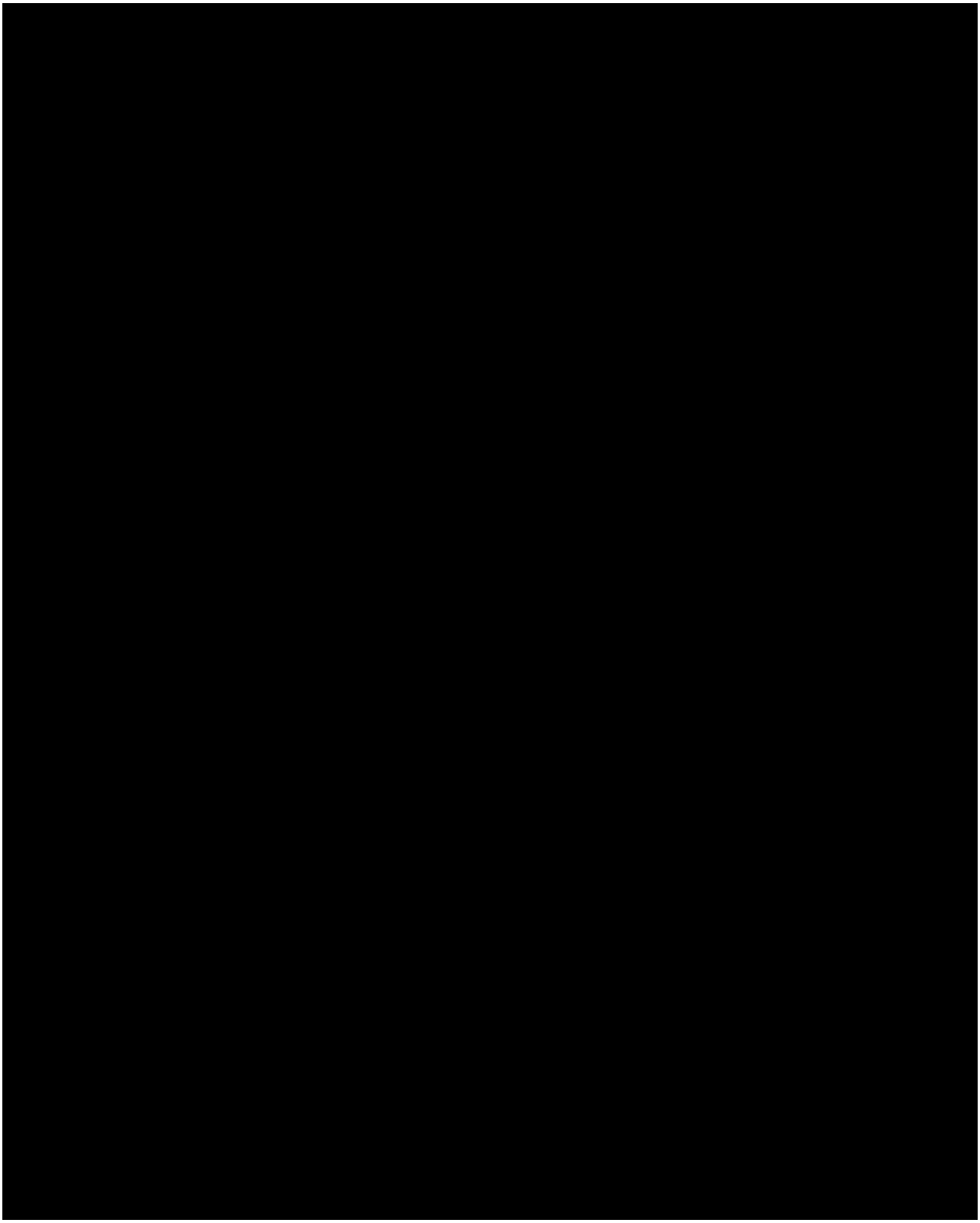
7.3.2.6.1 Electrocardiogram (ECG) and blood pressure

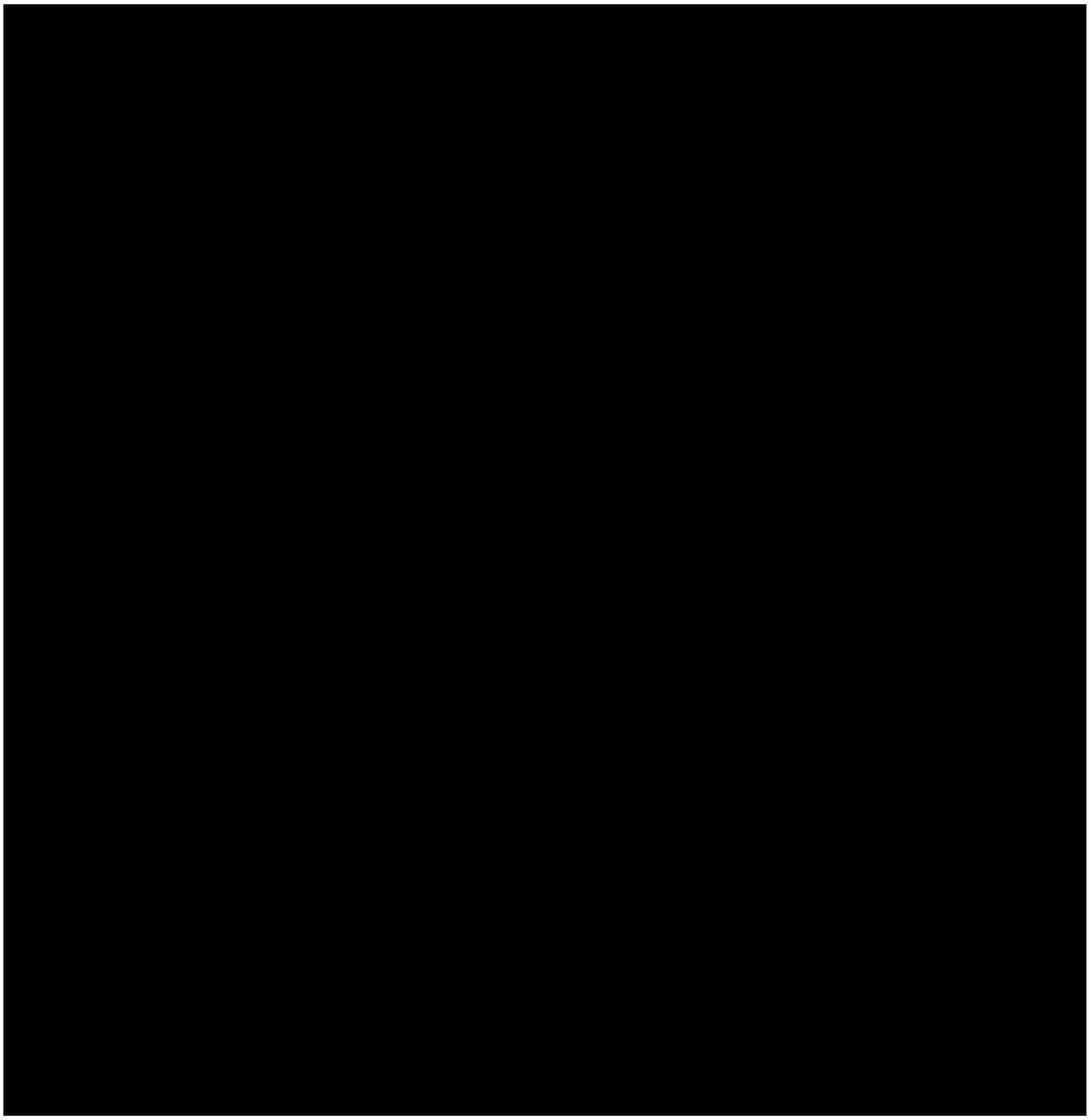
Standard 12-lead ECG assessment will be performed locally on **all** patients as per the schedule of assessments (Table 7-1). At screening, (as means of triplicate ECGs) ECGs will be assessed at C1, C2 and C3. For subsequent cycles, may be performed at the discretion of the investigator.

An ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated.

Interpretation of the tracing must be made by a qualified physician. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, ECG actual date, measured variables (QT), derived variables (QTcF, and HR) and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

[redacted]





7.3.5 Resource utilization

Not Applicable.

7.3.6 Patient reported outcomes

Not Applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death eCRF.

Abnormal laboratory values or test results occurring after signing the ICF constitute adverse events only if they induce clinical signs and symptoms, or require therapy, (e.g., any hematologic abnormality that requires transfusion of hematological stem cell support) or changes in medication(s) are considered clinical significant and should be recorded on the Adverse Event eCRF under signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinical significant (e.g. cause study discontinuation or constitute in and of itself a Serious Adverse Event) should be recorded on the Adverse Events eCRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)

[redacted]

4. Action taken with respect to study or investigational treatment (none, dose adjusted temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST 1.1 criteria for solid tumors, RANO and RECIST 1.1 criteria for GBM or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Whenever possible, a diagnosis should be reported instead of underlying signs and symptoms.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator’s discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest to be monitored for ceritinib have also been identified and include: hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations).

[redacted]

Details regarding these adverse events are provided in the [Investigator's Brochure] for ceritinib. Potential emergent new AEs will be monitored during the course of the study.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

[redacted]

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries

8.3 Emergency unblinding of treatment assignment

Not applicable. This is an open-label study.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis immediately (within 24 hours) of learning of its occurrence. Patients who become pregnant during the trial must be withdrawn. The pregnancy will be followed up from the estimated date of delivery plus 3 months to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis DS&E. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment. A pregnancy outcome informed consent will be provided by Novartis. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 3 months after treatment has been stopped.

[redacted]

If a pregnancy occurs while on study treatment, the newborn will be followed for at least 3 months.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements

and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

Electronic Data Capture (EDC) is used for this study. The designated investigator staff will enter the data required by the protocol into the electronic Case Report Forms (eCRFs). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator (PI) is responsible for assuring that the data entered into eCRFs is complete, accurate, and that entry and updates are performed in a timely manner.

Blood samples for biochemistry, ALK confirmatory testing [redacted] will be collected by sites and sent to a central laboratory for processing.

Blood samples for hematology tests will be processed and analyzed locally.

Radiological and ECG data will be acquired by the sites and interpreted locally.

In addition, data entered into IRT for screening, discontinuation, and patient identifiers (i.e. date of birth, gender, and patient ID) will be transferred electronically to Novartis as described in the Data Transfer Specification for designated IRT vendor.

[redacted]

[redacted]

9.4 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staffs are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). Data that will be processed centrally includes:

- IRT data including information regarding screening, subsequent drug assignments and discontinuation
- Centrally analyzed laboratory data including chemistry, [redacted]

Data about all study treatments dispensed to the patient will be tracked using IRT. The system will be supplied by the vendor(s), who will also manage the database. The data will be sent electrically to Novartis personnel.

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the data available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between Global Head of Biostatistics and Data Management and the Global Head of Clinical Development

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigative site.

[redacted]

10 Statistical methods and data analysis

10.1 Analysis sets

A patient is considered to be enrolled into the study if he/or she has signed informed consent. Only a patient who has signed informed consent will be included in the analysis data sets.

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who receive at least one dose of Ceritinib.

Unless otherwise specified the FAS will be the default analysis set used for all efficacy analyses, including the primary efficacy analysis.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication.

10.1.3 Per-Protocol Set

Not applicable.

10.1.4 Dose-determining analysis set

Not applicable.

[redacted]

10.1.6 Other analysis sets

Not applicable.

10.1.6.1 Efficacy/evaluable set

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for all patients by arm for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

[redacted]

10.3 Treatments (study treatment, concomitant therapies, compliance)

The actual dose and duration in days of ceritinib as well as the dose intensity (computed as the ratio of total dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity received/planned duration), will be listed and summarized for all patients by arm.

Dose reductions and dose interruptions delays (including the reasons for these) will be listed and summarized by arm.

The safety set will be used.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized for all patients by arm.

10.4 Primary objective

The primary objective is to assess the Disease Control Rate associated with ceritinib treatment based on local investigator assessment.

10.4.1 Variable

The variable used to evaluate the primary objective is Disease Control Rate associated with ceritinib treatment based on local investigator assessment. For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR or PR or SD $\geq$ 16 weeks after the first dose the study drug. For GBM, RANO and RECIST 1.1 response criteria will apply. For hematologic tumors, Cheson response criteria will apply.

10.4.2 Statistical hypothesis, model, and method of analysis

This study will contain 5 arms with ALK+ patients, an adaptive design will be used to assess activity of treatment in terms of response (DCR) rate within each arm and across each arm. The rules for how the trial adapts are pre-specified and are not based on ongoing data.

The design of the trial adapts to the data that are accumulated in the trial in such a way as to accommodate two possibilities:

a. DCR to ceritinib is specific to ALK+ inhibition and independent of the tumor site (similar DCR irrespective of tumor type);
b. the various tumor types have distinct DCR to ceritinib.

The pre-specified analysis is adaptive in the sense that when response depends on ALK+ inhibition and not on arm (scenario A), then it borrows from across the various arms and provide more precise estimate of DCR rates for those arms with similar response rates. In the other possibility (the various arms have distinct anti-tumor activity to ceritinib (Scenario B), the design allows little/no borrowing across tumor types. In this case the trial will be similar to traditional stratified analysis.

A hierarchical model (HM) will be used to analyze the binary data to facilitate the borrowing as specified above. Response rates (π_j) will be inferred for arm j (= 1,…,5). For each arm j, the number of responders follows a binomial distribution;

[redacted]

$$r_j \sim Bin(n_j, \pi_j)$$

We further let the parameters log (π_j/ (1 − πj)) (logistic transformation) be either exchangeable with some of the arms, or non-exchangeable with any of them. Based on the number of strata in this trial, we allow for two exchangeability distributions, which, for example, accounts for the case where some arm show no efficacy and some are promising.

Thus, for each arm j three possibilities arise, with respective probabilities $p_j = (p_{j1}, p_{j2}, p_{j3})$, as follows:

1. With probability p_{j1} the parameter θ_j follows a normal distribution with exchangeability parameters μ_1 and τ_1:

$$\theta_j \sim N(\mu_1, \tau_1^2)$$

2. With probability p_{j2}, θ_j follows a normal distribution with exchangeability parameters $\mu_1 < \mu_2$ and τ_2:

$$\theta_j \sim N(\mu_2, \tau_2^2)$$

3. With remaining probability $p_{j3} = 1 - p_{j1} - p_{j2}$, θ_j follows a weakly-informative prior distribution

$$\theta_j \sim N(m_w, v_w)$$

For the detailed specifications of m_w, v_w, the a-priori weights p_j (j=1,…,J), and the prior distributions for μ_1, τ_1, μ_2, and τ_2, see (Appendix 5). At any given time of the trial, including at the end, posterior probabilities of the various parameters will be estimated using Markov chain Monte Carlo methods.

For a specific disease group, a Proof of Concept about treatment with ceritinib will be declared if both of the following conditions are met:

a. Observed DCR ≥ "Disease Control Rate" threshold (column for C_2 in Table 10-1)
b. Posterior probability of "not being clinically meaningful" (column for C_1 in Table 10-1) is less than 20%

10.4.3 Handling of missing values/censoring/discontinuations

Confirmed partial or complete responses of stable disease reported prior to any additional anticancer therapy will be considered as responses in the calculation of the DCR irrespective of the number of missed assessments before response.

For solid tumor, patients with a best overall response of 'Unknown' or 'Not Assessed' per RECIST v1.1 will be considered as non-responders and will be included in the denominator in estimating the DCR. For GMB or hematologic tumor, patients with unknown or missing response, or who are treated in the study but provide no information on response at the end of treatment will be treated as non-responders and will be included in the denominator when calculating DCR.

10.4.4 Supportive analyses

Not applicable.

[redacted]

10.5 Secondary objectives

All secondary efficacy assessments (DOR, ORR, PFS, TTR) will be analyzed as per investigator assessment. Confirmation of response is required for all response endpoints, as per appropriate critetia (RECIST 1.1 for solid tumor, RANO and RECIST 1.1 for GMB, and Cheson for hematologic tumor)

All secondary analyses will be performed based on the FAS for each arm, unless otherwise specified.

No adjustment for multiple testing will be made.

10.5.1 Secondary objective(s)

Overall Response Rate

Overall Response Rate (ORR) is based on local investigator assessment per RECIST 1.1, RANO or Cheson criteria. For patients with solid tumors, the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For hematologic tumors, Cheson criteria will apply for evaluation of response and for GBM, RANO and RECIST 1.1 criteria will be used for response. ORR is defined as the proportion of patients with best overall response of CR, PR. For ORR, estimate and its 95% CI provided.

Duration of Response

Duration of Response (DOR) will be based on local investigator assessment per RECIST 1.1 for solid tumor, RANO and RECIST 1.1 for GBM, or Cheson criteria for hematologic tumors. Among patients with a confirmed response (PR or CR), DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause. If a patient has not had an event, DOR is censored at the date of last adequate tumor assessment. DOR will be listed by patient and may be described using Kaplan-Meier curves and relevant statistics if appropriate.

Time to response

Time to response (TTR) is defined as the time from the date of the first dose of LDK378 to first documented response (CR or PR, which must be confirmed subsequently) per appropriate critetia (RECIST 1.1 for solid tumor, RANO and RECIST 1.1 for GMB, and Cheson for hematologic tumor). TTR will be described using Kaplan-Meier methods and appropriate summary statistics. The TTR analysis will be conducted with censoring rules as described in the Appendix 2.

Progression-free survival

Progression-free survival (PFS) is defined as the time from the date of first dose of Ceritinib to the date of first documented disease progression per appropriate critetia (RECIST 1.1 for solid tumor, RANO and RECIST 1.1 for GMB, and Cheson for hematologic tumor) or death due to any cause.

A patient who has not progressed or died at the date of the analysis or when he/she receives any further anticancer therapy in the absence of disease progression will be censored at the

[redacted]

time of the last adequate tumor evaluation before the earlier of the cut-off date or the anticancer therapy date. By default, if disease progression or death is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression or death is documented after two or more missing tumor evaluations, the PFS time of these patients will be censored at the date of the last adequate tumor evaluation without PD.

If the study primary objective is not met (did not met Proof of Concept criteria) for a given arm, Novartis may decide not to conduct some of the above secondary efficacy analyses in that arn but instead may choose to provide those endpoints in listings only.

10.5.2 Other secondary efficacy objectives

Not applicable

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by arm and for all patients within the arm.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to **30** days after last dose of study medication
3. post-treatment period: starting at day **31** after last dose of study medication.

10.5.3.2 Adverse events (AEs)

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period. However, all safety data (including those from the pre- and post-treatment periods) will be listed and those collected during the pretreatment and post-treatment period will be flagged.

The incidence of AEs will be summarized by system organ class and/or preferred term, maximum severity (based on Common Terminology Criteria for Adverse Events [CTCAE] grades version 4.03), and relation to study drug.

Clinically notable adverse events (CNAEs) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment.

CNAEs SEC will be defined at the project level and may be regularly updated based on emergent data. For each specified CNAE SEC, number and percentage of patients with at least one event in each CNAE category will be reported

[redacted]

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Further details will be specified in the statistical analysis plan (SAP). Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

A listing of laboratory values will be provided by laboratory test, patient, and study day. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory abnormalities).

The following summaries will be generated separately for hematology and biochemistry laboratory tests:

- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

A separate listing will display notable laboratory abnormalities (i.e. newly occurring CTCAE grade 3 or 4 laboratory toxicities).

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the SAP.

10.5.3.4 Other safety data

Data from other tests (including ECGs and vital signs) will be summarized and listed, notable values will be flagged, and any other information collected will be listed as appropriate. Definitions of notably abnormal results will be provided in theSAP.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Tolerability will be summarized in terms of dose reductions or drug interruption or discontinuation due to an AE.

[redacted]

[redacted]

Data handling principles

10.5.5 Biomarkers

Not applicable

10.5.5.1 Outline of the data analysis

Not applicable

10.5.5.2 Data handling principles

Not applicable

10.5.5.3 Data analysis principles

Not applicable.

10.5.5.3.1 Analysis sets

Not applicable.

10.5.5.3.2 Basic tables, figures and listings

Not applicable.

10.5.5.3.3 Advanced analysis methods

Not applicable.

10.5.6 Resource utilization

Not applicable.

10.5.7 Patient-reported outcomes

Not applicable.

[redacted]

[redacted]

[redacted]

10.7 Interim analysis

Subjects will be continuously accrued and the data will be analyzed using a Bayesian hierarchical model mentioned in Section 10.4.2. Interim analysis for an arm will be performed when a predefined number of patients (5 for IMT or T2 and 10 for all other tumor type) are enrolled and have completed 16 weeks of follow-up after the first dose of study drug and have their responses confirmed by a subsequent assessment at least 4 weeks later. At each of these analyses, the current (posterior) probability that the response rate for each of the tumor types is greater than "clinically meaningful threshold (column for C_2 in Table 10-1)" will be determined.

These probabilities will be used to adapt the design. All available data will be used for analysis at the interim. However, a decision will be made only for arm with minimum number of pre-specified patients (a minimum of 5 patients in IMT arm or a minimum of 10 patients for any of the other arm). For a specific arm, a decision will be made based on the calculated probability as given below:

1. Accrual to an arm (having at least predefined number of subjects) will cease for futility if it is very unlikely (posterior probability <20%) that the response rate for the arm is "clinically meaningful" (≥column for C_2 in Table 10-1)
2. Otherwise, recruitment will be extended for 10 more patients in that arm (including IMT). Accrual to an arm will cease when its maximum planned sample size is reached (15 for IMT or T2 and 20 for each of other arms). The results within an arm will be regarded as positive if the accrual for the arm reaches maximum and the conditions for positive conclusion [Section 10.4.2] are satisfied.

Depending on enrollment and follow-up, there may be multiple interim analyses.

Table 10-1 Type of tumors of interest with definition of being clinically meaningful

Disease Code	Arm	#Patients† at Interim	Not Clinically meaningful (C_1)	Clinically meaningful (C_2)
T1	Anaplastic large cell lymphoma (ALCL)	10	≤40%	≥50%
T2	Inflammatory myofibroblastic tumor (IMT)	5	≤20%	≥30%
T3	Glioblastoma	10	≤10%	≥20%
T4	Inflammatory breast cancer	10	≤10%	≥20%
T5	Any other ALK+ tumor	10	≤10%	≥20%
† Extend recruitment for 10 more patients in each arm according to IA outcome [p(clinically meaningful)>20%].				

[redacted]

Note that if there are at least 5 patients of the same arm in "Any other ALK+ tumor, T5)" arm, then a separate arm will be opened for that specific tumor type leading to a total of 6 different arms. However, interim analysis for decision making will not be performed until there are 10 patients in each of the arm: "new tumor type" and modified "Any other ALK+ tumor".

10.8 Sample size calculation

The design of this study is adaptive in nature; hence, the final sample size is not fixed. A minimum of 10 and a maximum of 20 subjects in each arm T1, T3, T4 and T5 will receive treatment. For arm T2, the minimum and maximum sample size will be 5 and 15 respectively. Thus, the total sample size across all tumor types will be between 45 and 95. Assuming a 10% drop out rate, approximately 106 patients are planned to be enrolled in this study.

Subjects will be continuously accrued, and, the accumulated data will be analyzed at interim as described in Section 10.7. Based upon the results of any of these analyses, enrollment into one or more arms may be terminated.

The operating characteristics for this Bayesian Design are evaluated using simulation and are presented below. Simulation-based probability estimates (relative frequencies) of futility at interim, positive results at final analysis and average sample size for each arm in three scenarios are provided.

1. Scenario 1 (not clinically meaningful for all arms): The true rates of response for T1, T2, T3, T4, and T5 are 40%, 20%, 10%, 10%, and 10%; respectively;
2. Scenario 2 (clinically meaningful for all arms): The true rates of response for T1, T2, T3, T4, and T5 are 60%, 40%, 30%, 30%, and 30%; respectively;
3. Scenario 3 (clinically meaningful for T1 and T4 but not for others): The true rates of response for T1, T2, T3, T4, and T5 are 60%, 20%, 10%, 10% and 30%; respectively;

In all three cases it is assumed that accrual rates are in proportion 2:1:2:2:2 for the 5 arms (T1, T2, T3, T4, and T5). The type I error (false positive rate) of the adaptive design can be viewed as the probability estimate of a positive conclusion at final analysis in Scenario 1 (Table 10-2). The power of the adaptive design is defined as the probability estimate of positive conclusion at final analysis in Scenario 2 (Table 10-3).

The simulation results for Scenario 1, when the effect of Ceritinib is not-clinically meaningful (true response rates equal 40% and 20 % and 10% for T1 and T2 and for other 3 arms respectively), show that the probability of stopping at interim for futility varies from 41.7% to 59.9% for different arm. Probability of concluding positive trial at final analysis (i.e., crossed interim and maximum sample size reached) are 11.5%, 13.8%, 12.5%, 11.0%, and 11.0% for T1, T2, T3, T4, and T5 respectively. The overall sample size is approximately 67.

Table 10-2 Simulation results Scenario 1 (ceritinib inactive for all arms)

Arm	True CBR (%)	Probability of stopping at IA for futility (%)	Probability for positive conclusion in final analysis (%)	Average Sample Size
T1	40.0	59.3	11.5	14.1
T2	20.0	41.7	13.8	10.8
T3	10.0	59.9	12.5	14.0
T4	10.0	58.8	11.0	14.1
T5	10.0	59.7	11.0	14.0
Overall				67.0

The simulation-based results for Scenario 2 (Table 10-3), when the truth is that the effect of Ceritinib is clinically meaningful in all arms, illustrate that approximately 69% to 87% of the simulated trial outcomes are positive at final analysis (passes futility interim and reaches the maximum enrollment) for different arm. In addition, the average overall sample size is 91 subjects.

Table 10-3 Simulation results Scenario 2 (ceritinib active for all arms)

Arm	True CBR (%)	Probability of a stopping at IA for futility (%)	Probability for positive conclusion in final analysis (%)	Average Sample Size
T1	60.0	14.2	69.3	18.6
T2	40.0	8.6	77.8	14.1
T3	30.0	5.0	86.8	19.5
T4	30.0	4.6	86.4	19.5
T5	30.0	4.9	86.0	19.5
Overall				91.2

In order to illustrate the design behavior one addition scenario (Scenario 3) is explored. In Scenario 3 the effect of Ceritinib is clinically meaningful for arms T1, T5 and not-clinically meaningful for all other arms (Table 10-4). Table 10-4 shows reasonable operating characteristics (futility at interim and positive results at final analysis) under Scenario 3. The average overall sample size under this scenario is 78.

Table 10-4 Simulation results Scenario 3 (certinib active for T1 and T5 arms)

Arm	True CBR (%)	Probability of stopping at IA for futility (%)	Probability for positive conclusion in final analysis (%)	Average Sample Size
T1	60.0	15.1	71.3	18.5
T2	20.0	35.0	14.9	11.7
T3	10.0	52.2	10.8	14.8
T4	10.0	52.7	11.6	14.7
T5	30.0	13.4	81.0	18.7
Overall				78.4

[redacted]

10.9 Power for analysis of key secondary variables

Not applicable.

11 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.1 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.3 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.5 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

[redacted]

11.6 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.7 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.8 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1: List of prohibited concomitant medications and concomitant medications requiring caution for ceritinib for LDK378

Table 14-1 Prohibited medications that are strong inducers or inhibitors of CYP3A, or CYP3A substrates with narrow therapeutic index, or sensitive CYP2C9 substrates with narrow therapeutic index**

CYP2C9 substrates with narrow therapeutic index			
warfarin	phenytoin		
CYP3A4/5 substrates with narrow therapeutic index			
astemizole*	diergotamine	pimozide	alfentanil
cisapride*	ergotamine	quinidine*	terfenadine*
cyclosporine	fentanyl	tacrolimus	sirolimus
Strong CYP3A4/5 inhibitors			
Macrolide antibiotics:	**Antivirals:**	**Antifungals:**	**Others:**
clarithromycin	indinavir	itraconazole	conivaptan
telithromycin	lopinavir	ketoconazole	elvitegravir
troleandomycin	nelfinavir	posaconazole	mibefradil
	ritonavir	voriconazole	nefazodone
	saquinavir		
	tipranavir		
Strong CYP3A/5 inducers			
avasimibe	carbamazepine	phenobarbital	phenytoin
rifabutin	rifampin	St. John's wort	

* Compounds known to increase QTc interval that are also primarily metabolized by CYP3A4/5.

For an updated list of CYP2C9 substrates, CYP3A substrates, inhibitors and inducers, please reference the Novartis Oncology Clinical Pharmacology internal memo: drug-drug interactions (DDI) database, Oct 2010, which is compiled primarily from the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database.

**Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

[redacted]

Table 14-2 List of medications to be used with caution

CYP2C9 substrates			
losartan	irbesartan	diclofenac	ibuprofen
piroxicam	tolbutamide	glipizide	acenocoumarol
celecoxib	sulfamethoxazole	tolbutamide	torsemide
CYP3A4/5 substrates			
dronedarone	capravirine	aripiprazole	casopitant
alprazolam	ritonavir	haloperidol	quinine
diazepam	telaprevir	imatinib	tamoxifen
amlodipine	atorvastatin	nilotinib	tolvaptan
diltiazem	everolimus	methadone	trazodone
nifedipine	erythromycin	boceprevir	vincristine
nisoldipine		brecanavir	verapamil
nitrendipine			
Moderate CYP3A4/5 inhibitors			
ciprofloxacin	darunavir	grapefruit juice	dronedarone
erythromycin	fosamprenavir	aprepitant	tofisopam
amprenavir	diltiazem	casopitant	
atazanavir	verapamil	cimetidine	
Moderate CYP3A4/5 inducers			
bosentan	efavirenz	etravirine	modafinil
nafcillin	ritonavir	talviraline	tipranavir
Proton pump inhibitors			
esomeprazole	lansoprazole	omeprazole	pantoprazole
rabeprazole			

The list of CYP2C9 and 3A4/5 substrates, 3A4/5 inhibitors and inducers is from the Novartis Oncology Clinical Pharmacology internal memo: drug-drug interactions (DDI) database, Oct 2010, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (http://medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies".

Table 14-3 List of prohibited enzyme-inducing anti-epileptic drugs

Prohibited enzyme-inducing anti-epileptic drugs			
carbamazepine	ethotoin	felbamate	fosphenytoin
phenobarbital	phenytoin	primidone	topiramate

[redacted]

Table 14-4 List of prohibited QT prolonging drugs

Prohibited medications causing QTc prolongation			
Antiarrhythmic:	**Anticancer:**	**Antibiotic:**	**Antianginal:**
amiodarone	arsenic trioxide	azithromycin	bepridil
disopyramide	vavdetanib	clarithromycin*	**Antipsychotic:**
dofetilide	**Antihistamine:**	erythromycin*	chlorpromazine
flecainide	astemizole*	moxifloxacin	haloperidol*
ibutilide	terfenadine*	sparfloxacin	mesoridazine
procainamide	**Antimalarial:**	**Antinausea:**	pimozide
quinidine*	chloroquine	domperidone	thioridazine
sotalol	halofantrine	droperidol	**Opiate agonist:**
Antilipemic:	**Anti-infective:**	**GI stimulant:**	levomethadyl
probucol	pentamidine	cisapride*	methadone
Antidepressant:			
citalopram			

Please note: *CYP3A substrate

Source: Arizona Center for Education and Research on Therapeutics (CERT), Drugs that prolong the QT interval and/or induce Torsades de Pointes, http://.azcert.org/medical-pros/drug-lists/drug-lists.cfm

[redacted]

14.2 Appendix 2: Harmonization of efficacy analysis of solid tumor studies (RECIST 1.1)

Tumor assessments will be based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines (Eisenhauer 2009).

14.2.1 Measurability of tumor lesions at baseline

All tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

14.2.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

14.2.1.2 Non-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with >10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.2.1.2.1 Bone lesions

- B, PET and plain films are not adequate to measure bone lesions; they may be used to determine the presence or absence of a lesion.
- Lytic or lytic-blastic lesions with identifiable soft tissue component that can be measured by CT or MRI and meets size requirement can be considered measurable. Blastic bone lesions are non-measurable.

14.2.1.2.2 Cystic lesions

- Cystic lesions that meet the criteria for simple cysts are not measurable.
- Cystic lesions that are thought to be cystic metastatic disease can be considered measurable disease, however if non-cystic lesions are present in the same patient these are preferable to include as target lesions.

[redacted]

14.2.1.2.3 Lesions previously treated

- Lesions within radiotherapy ports or who have been subject to other loco-regional treatment are usually not considered to be measurable and will be allowed on this study only with approval of the sponsor.

14.2.2 Specification by methods of measurement

14.2.2.1 Measurement of lesions

All measurements should be taken and recorded in metric notation. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

14.2.2.1.1 Target lesions

All lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions. If the largest lesion does not lend itself to reproducible measurement, the next largest lesion which can be measured reproducibly should be selected.

Pathological lymph nodes which are measurable may be identified as target lesions if they have a short axis of >15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained. The smaller of these measures is the short axis. All other pathological nodes (those with short axis >10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

14.2.2.1.2 Non-target lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

14.2.2.2 Response criteria

14.2.2.2.1 Evaluation of target lesions

This section provides the definitions of the criteria used to determine overall tumor response for target lesions as shown below in Table 14-5.

[redacted]

Table 14-5 Evaluation of target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.[1]
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (Note: the appearance of one or more new lesions is also considered progression)
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Notes on the assessment of Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. In order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

14.2.2.2.2 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions as shown below in Table 14-6. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Table 14-6 Evaluation of non-target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

14.2.2.2.3 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded appropriately in the eCRF.

[redacted]

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which **was not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment.
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥10 mm for the first time in the study plus 5 mm absolute increase.
  a. Negative FDG-PET at baseline, with a positive[1] FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

14.2.2.2.4 Tumor markers

Tumors markers alone will not be used to assess overall response. If elevated at baseline, they must normalize for a patient to be considered as having a CR. For the purpose of this protocol, Cancer Antigen-125 (CA-125) will be used in the assessment of ovarian and Prostate Specific Antigen (PSA) will be used in the assessment of prostate.

14.2.3 Evaluation of best overall response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as indicated below in Table 14-7 and Table 14-8.

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence. The best overall response for CR and PR will be determined at 8 weeks as indicated below in Table 14-9.

[redacted]

Table 14-7 Point response: patients with target (+/- non-target) disease

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

Table 14-8 Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PR[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PR
Any	Yes	SD

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 14-9 Best overall response when confirmation of CR and PR required

Overall lesion response at first time point	Overall lesion response at subsequent time point	Best overall lesion response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD[b]
CR	PD	SD[b]
CR	NE	SD[c]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD[b]
PR	NE	SD[c]
NE	NE	NE

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether 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 time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Provided minimum criteria for SD duration met, otherwise, PD

[c] Provided minimum criteria for SD duration met, otherwise, NE

[redacted]

14.2.4 References (available upon request)

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14.3 Appendix 3: Response assessment in neuro-oncology (RANO) criteria for high-grade gliomas

Antitumor response will be primarily evaluated by the Response Assessment in Neuro-Oncology (RANO) working group (Wen et al 2010) criteria in this study. The RANO Criteria updates its established predecessor, the modified Macdonald Criteria (Macdonald et al 1990), by adding assessment of non-enhancing lesions.

Patients will undergo Contrast MRI assessments for response evaluation starting at Week 8 and every 8 weeks thereafter to evaluate brain lesions, as outlined in the Visit schedule Table 7-1 and Table 7-2.

The following components will be taken into account when assessing a patient's overall response at an individual evaluation.

- Tumor evaluation eCRF page for measureable enhancing lesions (T1-Gd+)
- Tumor evaluation eCRF page for non-measurable enhancing lesions (T1-Gd+)
- Tumor evaluation eCRF page for non-enhancing lesions (T2/FLAIR)
- Tumor evaluation eCRF page for new lesion
- Concomitant medication eCRF page for steroid usage
- Clinical status eCRF page for KPS and other clinical evaluation finding
- Overall response eCRF page for response category (CR/PR/PD/SD/NA)

14.3.1 Antitumor effect - definitions

Evaluable for toxicity

All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response

Only those participants who have measurable disease present at baseline (cycle 1, day 1 scan) and have received at least one dose of therapy will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

Measurable disease

Bidimensionally, contrast-enhancing, measurable lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 10mm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are multiple measurable lesions, the investigator must choose a minimum of two and a maximum of five of the largest lesions to be followed before a participant is entered on study. The remaining lesions will be considered non-measureable for the purpose of objective response determination. Unless

progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

Non-measurable evaluable disease

Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 10mm.

14.3.2 Response/progression categories

Complete response (CR)

All of the following criteria must be met:

a. Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No new lesions.
c. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
d. Participants must be on no steroids or on physiologic replacement doses only.
e. Stable or improved non-enhancing (T2/FLAIR) lesions
f. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related

Participants with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial response (PR)

All of the following criteria must be met:

a. Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No progression of non-measurable disease.
c. No new lesions.
d. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e. The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
g. Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.

Participants with non-measurable disease cannot have a partial response. The best response possible is stable disease.

[redacted]

Progressive disease (PD)

The following criterion must be met:

a. 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response or baseline if no decrease) on stable or increasing doses of corticosteroids **and/or one or more of the of the following:**

b. Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids steroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).

c. Any new lesion

d. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose.

e. Failure to return for evaluation due to death or deteriorating condition.

f. Clear progression of non-measurable disease

Stable disease (SD)

All of the following criteria must be met:

a. Does not qualify for CR, PR, or progression.

b. All measurable and non-measurable sites must be assessed using the same techniques as baseline.

c. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

d. Stable clinically.

Unknown response status

Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

These RANO Response Criteria are also summarized in Table 14-10:

[redacted]

Table 14-10 Summary of the RANO response criteria

	CR	PR	SD	PD#
T1-Gd +	None	≥50% decrease	<50% decrease but <25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA**
Clinical Status	Stable or improve	Stable or improve	Stable or improve	Deterioration*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease
*: Progression when this criterion is met **: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

14.3.3 Methods for evaluation of measurable disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

14.3.4 Evaluation of best response

The best overall response is the best response recorded from the start of the treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started). If a response recorded at one scheduled MRI does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, i.e. still present on the subsequent MRI, it will be recorded as a sustained response, lasting until the time of tumor progression. Participants without measurable disease may only achieve SD or PD as their best "response."

14.3.5 Other effect measures

14.3.5.1 Neurological exam

Although not used for determining response, it is useful to evaluate changes in the neurological exam compared to the previous exam. The following scale may be used:

+2 Definitely better
+1 Possibly better
0 Unchanged
-1 Possibly worse
-2 Definitely worse

[redacted]

14.3.5.2 Performance status

Participants will be graded according to KPS score

14.3.5.3 Overall survival time

From date of first dose (date of first post-surgery treatment for participants in Dose Level 1) to date of death due to any cause.

14.3.5.4 Progression-free survival time:

From date of first dose (date of first post-surgery treatment for participants in Dose Level 1) to date of progression or death. Participants who stop treatment for causes other than progression may be censored if other therapy is initiated or if regular assessments for assessing progression are no longer available.

[redacted]

14.4 Appendix 4: Guidelines for efficacy evaluation in lymphoma studies (based on Cheson response criteria). International Working Group guidelines for hematological malignancies

Disease assessments will be based on the International Working Group response criteria (Cheson 1999), and the International Harmonization Project revised response criteria (Cheson et al 2007b). Further clarification on these criteria has been published by (Cheson 2007a).

14.4.1 Definitions and criteria for normalization

14.4.1.1 Definitions

14.4.1.1.1 Nodal vs extranodal lesion

A lesion is categorized based on the location as:

- **Nodal lesion,**
- **Extranodal lesion**, if it is located in organs other than lymph node or nodal mass, but including spleen and liver.

14.4.2 Measurability of tumor lesions at baseline

All tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

14.4.2.1 Measurable nodal and extranodal lesions

A lesion will be called **measurable** if it can be measured accurately in 2 perpendicular dimensions and:

- For nodal lesion, if the long axis is > 15 mm, regardless of the length of the short axis,
- For extranodal lesion, if the long and short axes are ≥ 10 mm.

Patients should have at least one measurable nodal lesion greater than 20 mm in the long axis. In cases where the patient has no measurable nodal lesions greater than 20 mm in the long axis at Screening, then the patient must have at least one measurable extranodal lesion.

14.4.2.2 Classification of lymph nodes

Lymph nodes are classified according to their size and/or relationship to the disease:

- A lymph node meeting the measurability requirement above will constitute a **measurable nodal lesion**.
- A lymph node not meeting the measurability requirement but with long axis > 15 mm (e.g. short axis cannot be measured accurately) will constitute a **non-measurable nodal lesion**.
- A lymph node not meeting the measurability criteria but with a size of 11 mm to 15 mm in the long axis and > 10 mm in the short axis will be checked for relationship to disease:
  - If it is thought to be disease related, it will constitute a **non-measurable nodal lesion**.

[redacted]

- If it is not thought to be disease related, it will constitute an **abnormal lymph node** but not a lesion.

- All other lymph nodes will be considered normal and will not constitute nodal lesions.

14.4.2.3 Criteria for normalization of lesions

The normalization of lesions is defined as follow:

- A measurable nodal lesion must become ≤ 15 mm in long axis to be considered normalized.
- A non-measurable nodal lesion must decrease to ≤ 10 mm in the short axis and be ≤ 15 mm in long axis to be considered normalized.
- An extranodal lesion must disappear completely (assigned a size of 0 mm x 0 mm) to be considered normalized.

14.4.3 Specification by methods of measurement

14.4.3.1 Measurement of lesions

All radiological measurements should be taken in two perpendicular dimensions and recorded in metric notation, using a ruler or calipers.

14.4.3.1.1 PET

Visual assessment currently is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary.[1] In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff.[1] Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate- or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen.

14.4.3.1.2 CT scan (or MRI)

For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at Screening and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If at Screening a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will

[redacted]

result by default in an "Unknown" overall radiological response assessment. However, another overall radiological response than the Novartis calculated "Unknown" response may be accepted from the investigator if a definitive overall radiological response can be justified to be based on the available information.

In order to calculate the sum of the product of the diameters (SPD) of all index lesions (or extranodal lesions), their size must be entered throughout the study.

Actual lesion measurements should be entered on the corresponding eCRFs. If, during the course of the study, either of the perpendicular diameters of a lesion cannot be reliably measured because of its small size, it is recommended to enter the minimum limit of detection as the diameter size (e.g. 5 mm for spiral CT). In other cases when, during the course of the study, the diameter cannot be reliably measured for reasons other than its size (i.e. borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

If lesions become confluent over time, it is recommended to measure them as one lesion, report the overall diameters to one of the lesions and assign 0 mm x 0 mm to each of the other previously measured lesions. If a lesion splits during the study, each sub-lesion should be measured separately for all subsequent assessments and all sub-lesions contribute to the SPD.

14.4.3.1.3 Bone marrow assessment

Documentation of status of bone marrow involvement by lymphoma based on prior bone marrow biopsy or aspirate findings is required at Screening for all patients.

If no such documentation is available then a bone marrow biopsy or aspirate should be performed at Screening.

If bone marrow involvement is assessed by biopsy, the biopsy sample should have a goal of > 20 mm unilateral core. If the biopsy sample is indeterminate by morphology (immunohistochemistry), then flow cytometry may be performed on bone marrow aspirate to confirm the findings.

14.4.3.1.4 Physical examination and assessment of B-symptoms

Skin lesions, if the size is ≥ 20 mm in at least one diameter, must be histologically confirmed for lymphoma involvement (the investigational site must document the histological confirmation (yes or no) on the corresponding eCRF) and photographed including a ruler (color photography using digital camera). Tumor assessment will be performed and results will be recorded on the corresponding eCRF at Screening and at Day 1 of every cycle (±4 days) after first dose of study drug.

B-symptoms are of importance in determining prognosis and should resolve completely in patients who have achieved complete response. B-symptoms in lymphoma patients are disease related clinical symptoms and are not caused by anticancer therapy (or drug toxicity).

B-symptoms are defined as follows:

- Significant unexplained fever (≥ 38°C),
- Unexplained, recurrent drenching night sweats

[redacted]

- Unexplained loss of > 10% body weight within the previous 6 months, as assessed and reported (present vs. absent) by the Investigator.

14.4.4 Evaluation of radiological response

For the sake of simplicity, complete remission and complete response will both be referred to as complete response.

Definitions of Response for Lymphoma patients are listed in Table 14-11. To evaluate disease response to treatment, all index and non-index lesions will be followed and assessed throughout the study. At each assessment, response is evaluated separately for the **index lesions** (Table 14-14) and **non-index lesions** (Table 14-13) identified at Screening, then a combined overall radiological response is determined (Table 14-16).

[redacted]

Table 14-11 Response definition for lymphoma

Response	Definition	Nodal Masses	Spleen. Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a. FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b. Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochem is try should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes a. FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site b. Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a. FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET b. Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

14.4.4.1 Evaluation of index lesions (nodal and extranodal)

14.4.4.1.1 When index nodal lesions are not in complete response

The response for index lesions is evaluated by calculating the Sum of the Products of Diameters (SPD) of all index lesions (see Table 14-12), except when there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions) (see Section 14.4.2.3).

[redacted]

Table 14-12 Radiological status based on SPD calculation for all index lesions

Response Criteria[1]	Evaluation of index lesions
Complete Response (CR)	See Table 14-14 below (not based on SPD calculation for all index lesions)
Partial Response (PR)	At least 50% decrease from Screening in the SPD of all index lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD
Progressive Disease (PD)	At least a 50% increase from nadir[2] in the SPD of all index lesions

[1] At each assessment (if the index nodal lesions are not in CR status), the response status based on SPD calculation will be first assessed for meeting PD status criteria, then PR status and SD status.
[2] Nadir is defined as the smallest sum of the product of the diameters of all index lesions recorded so far, at or after Screening.

14.4.4.1.2 When index nodal lesions are in complete response

When there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions as defined in Section 14.4.2.3: all index lesion ≤ 15 mm in long axis), the SPD for these index nodal lesions may not be equal to zero and therefore a calculation of a SPD for all index lesions may be misleading. Therefore, by default, a specific response for extranodal index lesions needs to be evaluated, based on the SPD calculation restricted to all index extranodal lesions only (see Table 14-8).

Table 14-13 Radiological response criteria for index extranodal lesions in case of CR in index nodal lesions

Response Criteria[1]	Evaluation of index extranodal lesions
Complete Response (CR)	Complete disappearance of all index extranodal lesions
Partial Response (PR)	At least 50% decrease from Screening in the SPD restricted to all index extranodal lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD
Progressive Disease (PD)	At least a 50% increase from nadir[2] in the SPD restricted to all index extranodal lesions

[1] At each assessment, response will be first assessed for meeting CR status. If CR status is not met, response will be assessed for PD status, then PR status and SD status.
[2] Nadir is defined as the smallest sum of the product of the diameters restricted to all index extranodal lesions recorded so far, at or after Screening.

The algorithm for evaluating the response integrating index extranodal lesions and the SPD calculated on all index lesions (where appropriate) provides an overall response for index lesions.

14.4.4.1.3 Evaluation of response for all index lesions

The evaluation of response for all index lesions is based on the combination of the response for index nodal lesions (CR or non-CR), the response for index extranodal and the status based on the SPD calculated on all index lesions (nodal and extranodal), as described in Table 14-14.

[redacted]

Table 14-14 Radiological response for index lesions

Response for index nodal lesions[1]	Response for index extranodal lesions[1]	Status based on SPD calculation for all index lesions	Response for index lesions
CR	CR	Not calculated	CR
CR	SD/ PR	Not calculated	PR
CR	PD	PD	PD
CR	PD	PR	PR
CR	PD	SD	SD
Non-CR	Not evaluated	PD	PD
Non-CR	Not evaluated	PR	PR
Non-CR	Not evaluated	SD	SD

[1] If no index nodal lesions are present at Screening, then index lesions response is equal to the index extranodal lesions response. A similar rule applied if no index extranodal lesions are present at Screening, then index lesions response is equal to the index nodal lesions response.

In case of missing measurements of any of the index lesions, the radiological response for index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.

All lesions must have been measured with the same method as the one used at Screening, otherwise the radiological response for index lesions at that assessment will be "Unknown (UNK)".

14.4.4.1.4 Evaluation of non-index lesions (including nodal, splenic and/or hepatic nodules and other extranodal lesions)

At each reassessment, a non-index lesion (or a group of non-index lesions) will be given one of the following designations:

- Normalization (non-index nodal lesion has regressed to normal size; non-index extranodal lesion is no longer present). Normalization of non-index nodal lesions should be determined based on their size at Screening.
- Improved, stable or worsened, but without unequivocal evidence of disease progression (non-index lesion is present but there is not sufficient worsening to declare PD based on the existing non-index lesions).
- Unequivocal evidence of disease progression (worsening of existing non-index lesions is sufficient to declare PD).
- Not assessed.

Then, this status for each non-index lesion (or group of non-index lesions) will lead to a global response for non-index lesions (Table 14-15):

[redacted]

Table 14-15 Response criteria for non-index lesions (nodal, splenic and/or hepatic nodules and other extranodal lesions)

Response Criteria	Evaluation of non-index lesions
Complete Response (CR)	Complete normalization of all non-index nodal and extranodal lesions: Radiological regression to normal size of all lymph nodes and complete disappearance of all extranodal (including splenic and/or hepatic nodules) lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR and failure to fulfill the criteria for PD
Progressive Disease (PD)	Unequivocal disease progression of any existing non-index lesions (nodal or extranodal)

In case of a missing status of any of the non-index lesions, the radiological response for non-index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.

All lesions must have been measured with the same method as the one used at Screening, otherwise the radiological response for non-index lesions at that assessment will be "Unknown (UNK)".

14.4.4.2 New lesions

The appearance of

- any new nodal lesion >15 mm in any axis. New nodal lesion is defined by:
  - either a previously normal lymph node becoming > 15 mm in any axis,
  - or a previously identified abnormal lymph node showing an increase of at least 50% in the long axis,
  - as assessed by investigator

OR

- any discrete extranodal (including splenic and/or hepatic nodules) lesions reliably appearing on CT scan or MRI after Screening.

is always considered as Progressive Disease (PD) and has to be recorded as a new lesion in the appropriate module of the eCRF. Determination of new lymphoma involvement in organs other than lymph nodes or liver or spleen should be confirmed histologically and the site must document that in a comment to the corresponding eCRF.

14.4.4.2.1 Overall radiological response

Overall radiological response is calculated as shown in Table 14-16.

[redacted]

Table 14-16 Overall radiological response at each assessment

Index lesions	Non-index lesions[1]	New lesions	Overall radiological response
CR	CR	No	CR
CR	SD	No	PR
PR	CR or SD	No	PR
SD	CR or SD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1] If no non-index lesions are present at Screening, then this column is not used in evaluating overall radiological response.

If the evaluation of any of the index or non-index lesions identified at Screening could not be made during follow-up or if the index or non-index response is "Unknown (UNK)", the overall response status at that assessment must be "Unknown (UNK)" unless progression or a new lesion was seen.

14.4.4.2.2 Evaluation of overall disease response

The evaluation of overall disease response at each assessment is a composite of the individual radiological responses (index and non-index lesions, new lesions), laboratory test (bone marrow) and clinical responses (lymphoma related clinical symptoms).

14.4.4.2.3 Bone marrow re-assessment at time of radiological CR

In order to confirm a Complete disease response (CR), bone marrow biopsy or aspirate may be required when a radiological CR has been achieved. Details are provided in the Study Protocol. The infiltrate of lymphoma in bone marrow must have cleared on repeat bone marrow biopsy or aspirate. Patients who achieve a CR by other criteria but who have persistent morphologic positive or inconclusive bone marrow involvement will be considered partial responders. New or recurrent bone marrow involvement anytime during the follow up will be considered PD. Bone marrow biopsy or aspirate will be performed after the first assessment of CR or when clinically indicated.

The biopsy sample of bone marrow must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry.

14.4.4.2.4 Overall disease response

If a patient has an overall radiological response of CR then this response must be confirmed by bone marrow biopsy or aspirate (if required as per the Study Protocol), presence of normal liver and spleen size, and evaluation of lymphoma related B-symptoms. The patient's overall response will be calculated as follows:

A patient will be deemed to have overall disease response of CR if bone marrow biopsy or aspirate becomes negative for tumor involvement (if the bone marrow was involved by lymphoma at Screening) and the liver and spleen are normal in size and there are no lymphoma related B-symptoms in addition to radiological CR.

[redacted]

If assessments of any of the following: lymphomatous infiltration of bone marrow (If required as per the Study Protocol), or evaluation of B-symptoms is not done, unknown or indeterminate or B-symptoms are still present when the overall radiological response is assessed as CR or the liver or spleen are enlarged, then the overall disease response will be assessed as PR until evaluation of these factors have shown normalized results and recorded on the corresponding eCRF.

For patients whose radiological response is anything other than CR, assessment of bone marrow, liver, spleen and B-symptoms will not be required in evaluating overall response and overall disease response is the same as radiological response. However any new or recurrent bone marrow involvement at any time during follow-up will be considered PD.

Of note, appearance of B-symptoms or enlarged spleen or liver will not in themselves constitute documentation of progression. They are however expected to be associated with progressive disease. Every effort should be made to document that evidence radiologically and report the corresponding tumor assessments. Such tumor assessments are expected to be performed within 2 months of appearance of B-symptoms or enlarged spleen or liver.

14.4.5 References (available upon request)

Cheson BD (2007a) The international harmonization project for response criteria in lymphoma clinical trials. Hematol Oncol Clin N Am 21:841-854.

Cheson BD (2009) The case against heavy PETing. J Clin Oncol 27:1742-1743.

Cheson BD, Horning SJ, Coiffier B, et al (1999) Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 17:1244-1253.

Cheson BD, Pfistner B, Juweid ME, et al (2007b) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586.

FDA Guideline (2005) Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

14.5 Appendix 5: Details statistical methodology

This section provides the details of model stated in Section 10.4.2. Prior specifications of model parameters are provided in details. Data analysis and decision making in real trial are illustrated using some hypothetical data scenarios. Further operating characteristics by simulation are provided in Section 10.8 as part of sample size justification.

14.5.1 Prior specification of model parameters

Bayesian model requires prior specification of parameters. The detailed prior specification of μ_1, μ_2,τ_1, τ_2, m_w, v_w, and p_j (j= 1,2,..,5) are described in this section.

14.5.1.1 Prior specification of exchangeability distribution (μ_1, μ_2, τ_1 and τ_2)

Prior for τ_1 and τ_2 are assumed to be half-normal distribution with scale 0.25, implying a prior 95%-interval for τ_1 and τ_2 as (0.008, 0.560), which allows for small to substantial between strata heterogeneity (see Spiegelhalter et al 2004).

μ_1 and μ_2 are given normal prior distributions. For first exchangeability distribution μ_1, the mean of the prior distribution ($m_{\mu 1}$) is set to logit(0.15) (or $m_{\mu 1}$= log(1/3)) which corresponds to no treatment effect. For second exchangeability distribution μ_2, the prior mean ($m_{\mu 2}$) was set to logit(0.6) (or $m_{\mu 1}$= log(3/2)). This corresponds to a substantial treatment effect. The variance parameter ($V_{\mu 1}$ and $V_{\mu 2}$) are derived using the following formula from law of total variance

$$V_{\mu i} = V(\theta) - E(\tau_i^2) \text{ and } V(\theta)=1/\pi + 1/(1- \pi) \text{ ; } \pi= 0.15, 0.60 \text{ and } i=1,2$$

This yields $V_{\mu 1}$= 7.780 ($\approx 2.789^2$) and $V_{\mu 2}$= 4.101 ($\approx 2.025^2$). This allows a considerable uncertainty on prior belief of θ.

14.5.1.2 Prior specification for stratified or "non-exchangeability" distributions (m_w and v_w)

The strata-specific normal priors for the stratified or "non-exchangeable" case are defined by m_w and v_w were. The prior median for the response probability was set as 10% (no treatment effect) i.e., m_w=logit(0.1) (or m_w = log(1/9)) and the corresponding variance (v_w) is set to 9 ($=3^2$) to allow large variability in prior.

14.5.1.3 Specification of mixture weights (p_j)

Finally, for each stratum j, the prior mixture weights p_j were chosen as

$$p_j = (0.25, 0.25, 0.50), \qquad j=1,\ldots,5.$$

This means that each stratum has 25% prior probability to belong to the first exchangeability distribution (μ_1 and τ_1), 25% probability to belong to the second exchangeability distribution (μ_2 and τ_2), and 50% probability to be stratified or non-exchangeable with some (or all) of the other strata.

The prior distributions are summarized in Table 14-17, which also shows the prior medians and 95%-intervals for the disease specific disease control rare (DCR) π_j.

[redacted]

Table 14-17 Specifications for model parameters, and prior median (95%-interval) for disease specific DCR

Parameter	Prior distribution
μ_1	N(-1.735, 2.789^2)
μ_2	N(0.405, 2.025^2)
τ_1	Half Normal(scale=0.25)
τ_2	Half Normal(scale=0.25)
m_j, v_j	N(-2.197, 3^2)
$p_j = (p_{j1},p_{j2},p_{j3})$, j=1,…,5	(0.25, 0.25, 0.5)
Prior disease specific DCR	median (2.5%, 97.5%)
π_j, j=1,…,5	0.218 (0.001, 0.981)

14.5.2 Hypothetic scenario testing

It is important to know that the design should make reasonable decisions at interim and final analysis based on the observed responses in each tumor type. This section shows on-study decisions made under the model and prior for the specified DLT observations. The hypothetical data scenarios for interim and final analysis can be found in Table 14-2 and Table 14-3 respectively. For each scenario, the probability of being "clinically meaningful" and "not clinically meaningful" (Table 10-1) are calculated by tumor type and displayed in the tables.

Table 14-18 shows 6 different scenarios for interim analyses. As stated in Section 10.7 at interim a tumor type is stopped if the probability of being "clinically meaningful" is less than 20%. At interim if no arm or tumor type shows any activity (scenarios 1 and 2) the decision based on model based inference are reasonable. The posterior probabilities of "clinically meaningful" are less than 20% for all tumor type in both scenarios (Column 6 of Table 14-18). Similarly for scenarios 3 and 4 where all tumor types show some clinically meaningful activity the proposed decision rule suggests to "continue" all arms (posterior probability of "clinically meaningful" > 20%). The proposed design also shows reasonable decision for mixed scenarios (5 and 6). For example, under scenario 4, data for arms T3 and T5 show no clinically activity but the rest shows some activity. Based on the calculated probability of being clinically meaningful, the design allows correctly stopping (probability<0.20) for T3 and T5 at the interim while continues for the other arms.

[redacted]

Table 14-18 Hypothetical data scenarios and decision at interim

Scenario	Arm (Tumor Type)	No of responder/ No. of patients	Observed CBR	Posterior probability of not clinically meaningful †	Posterior probability being clinically meaningful †	Decision‡
1	T1	3/10	30%	0.8595	0.0468	Stop
	T2	1/5	20%	0.6005	0.1900	Stop
	T3	1/10	10%	0.4498	0.1878	Stop
	T4	1/10	10%	0.4685	0.1808	Stop
	T5	1/10	10%	0.4615	0.1755	Stop
2	T1	3/10	30%	0.8450	0.0550	Stop
	T2	1/5	20%	0.6223	0.1800	Stop
	T3	1/10	10%	0.4898	0.1743	Stop
	T4	1/10	10%	0.4833	0.1813	Stop
	T5	0/10	0	0.8620	0.0265	Stop
3	T1	7/10	70%	0.0843	0.7580	Continue
	T2	2/5	40%	0.1475	0.6390	Continue
	T3	3/10	30%	0.0298	0.7970	Continue
	T4	3/10	30%	0.0250	0.7980	Continue
	T5	2/10	20%	0.1128	0.6083	Continue
4	T1	8/10	80%	0.0198	0.9273	Continue
	T2	2/5	40%	0.1515	0.6040	Continue
	T3	3/10	30%	0.0253	0.7965	Continue
	T4	3/10	30%	0.0303	0.7925	Continue
	T5	2/10	20%	0.1135	0.6063	Continue
5	T1	7/10	70%	0.0373	0.8870	Continue
	T2	4/5	40%	0.0028	0.9835	Continue
	T3	1/10	10%	0.4983	0.1883	Stop
	T4	3/10	30%	0.0665	0.6865	Continue
	T5	1/10	10%	0.5123	0.1818	Stop
6	T1	7/10	70%	0.0290	0.8778	Continue
	T2	4/5	40%	0.0028	0.9870	Continue
	T3	1/10	10%	0.5538	0.1775	Stop
	T4	4/10	40%	0.0090	0.9138	Continue
	T5	0/10	0	0.9118	0.0168	Stop

† Calculated using a Bayesian hierarchical model mentioned in Section 10.4.2.
‡ A tumor type will be **stopped** if posterior probability being clinically meaningful is less than 20%.

Similar to interim Table 14-19 shows 5 different hypothetic scenarios for final analyses in order to illustrate final decision making process in the proposed design. As stated in Section 10.4.2 at final a Proof of Concept (PoC) about treatment with ceritinib will be declared for an arm (tumor type) if both of the following conditions are met:

a. Observed DCR ≥ "Disease Control Rate" threshold (Table 10-1)
b. Posterior probability of "not being clinically meaningful" (Table 10-1) is less than 20%

[redacted]

If no arm shows any significant activity (scenario 1) at final analysis the decision using model based inference are reasonable (declared fail to support PoC for all arms). The posterior probabilities of "not clinically meaningful" are less than 20% for all arms in this scenario (Column 5 of Table 14-19) but the observed CBR's do not cross "clinically meaningful" threshold (as stated in Table 10-1). Similarly for scenario 2 where all arms show clinically meaningful activity the proposed decision rule (to declared success) leads to PoC for all arms (posterior probability of "not clinically meaningful" < 20% and observed CBR's are more than "clinically meaningful" threshold). The proposed design also shows reasonable decision for mixed scenarios (3, 4, and 5). For example, under scenario 4, data for arms T1 and T3 show no clinically activity but the rest of the arms show activity. Based on the posterior probability of being not clinically meaningful and observed CBR, the design correctly declared fail for T1 and T3 while success for the other arms.

[redacted]

Table 14-19 Hypothetical data scenarios and decision at final

Scenario	Arm (Tumor Type)	No of responder/ No. of patients	CBR at final	Posterior probability of not clinically meaningful †	Posterior probability being clinically meaningful †	Decision‡
1	T1	8/20	40%	0.6133	0.1283	Fail
	T2	3/15	20%	0.6155	0.1330	Fail
	T3	2/20	10%	0.4678	0.0958	Fail
	T4	2/20	10%	0.4588	0.0968	Fail
	T5	2/20	10%	0.4670	0.0980	Fail
2	T1	14/20	70%	0.0125	0.9318	Success
	T2	6/15	40%	0.0550	0.6570	Success
	T3	6/20	30%	0.0048	0.8395	Success
	T4	4/20	20%	0.0500	0.6040	Success
	T5	4/20	20%	0.0500	0.6153	Success
3	T1	6/20	30%	0.9113	0.0113	Fail
	T2	415	40%	0.3198	0.2733	Fail
	T3	2/20	10%	0.4145	0.1703	Fail
	T4	5/20	25%	0.0255	0.6825	Success
	T5	1/20	5%	0.7243	0.0490	Fail
4	T1	8/20	40%	0.5765	0.1283	Fail
	T2	9/15	60%	0.0013	0.9800	Success
	T3	1/20	5%	0.7740	0.0403	Fail
	T4	6/20	30%	0.0040	0.8988	Success
	T5	5/20	25%	0.0205	0.7753	Success
5	T1	14/20	70%	0.0063	0.9500	Success
	T2	9/15	60%	0.0003	0.9810	Success
	T3	6/20	30%	0.0100	0.7983	Success
	T4	4/20	20%	0.0950	0.4938	Success
	T5	2/20	10%	0.4188	0.1608	Fail

† Calculated using a Bayesian hierarchical model mentioned in Section 10.4.2.

‡ A tumor type will be declared "**Success**" if posterior probability of being not clinically meaningful is less than 20% and observed CBR is at least clinically meaningful threshold.

[redacted]