NOVARTIS

Clinical Development

Ceritinib (LDK378)

Oncology Clinical Trial Protocol CLDK378A2205 / NCT02336451

A Phase II, multi-center, open-label, five-arm study to evaluate the efficacy and safety of oral ceritinib treatment for patients with ALK-positive non-small cell lung cancer (NSCLC) metastatic to the brain and/or to leptomeninges

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List of abbreviations

AE	Adverse event
µg	Microgram
AJCC	American Joint Committee on Cancer
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALKi	Anaplastic lymphoma kinase inhibitor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration versus time curve
AUC0-24h	Area under the plasma concentration versus time curve from time zero to 24 hours
AUCinf	Area under the plasma concentration versus time curve from time zero to infinity
AUClast	Area under the concentration-time curve from time zero to the last measurable concentration time
AUCtau	Area under the plasma concentration versus time curve from time zero to end of dosing period
BBB	Blood Brain Barrier
BIRC	Blinded Independent Review Committee
BLRM	Bayesian logistic regression model
BM	Brain metastases
BUN	Blood Urea Nitrogen
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
Cmax	Maximum (peak) concentration of drug in plasma
Cmin	Minimum (trough) concentration of drug in plasma
CMO&PS	Chief Medical Office & Patient Safety
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine Clearance
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
D	Entered into database
DBP	Diastolic blood pressure
DCR	Disease control rate
DHEA	Dihydroepiandrosterone
DILI	Drug Induced Liver Injury
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DMPK	Drug metabolism & pharmacokinetic
DOER	Duration of extracranial response
DOIR	Duration of intracranial response

[redacted]

DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDCR	Extracranial disease control rate
EGFR	Epidermal growth factor receptor
EIAED	enzyme inducing anti-epileptic medication
EML4-ALK	Echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase
EOS	End of study
EOT	End of treatment
eSAE	Electronic Serious Adverse Event
FAS	Full analysis set
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
GCP	Good Clinical Practice
HA	Health Authorities
hCG	human chorionic gonadotropin
HED	Human equivalent dose
Hgb	Hemoglobin
IB	Investigator's brochure
IC50	Half maximal (50%) inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IDCR	Intracranial disease control rate
IEC	Independent Ethics Committee
IGF1R	Insulin-like Growth Factor 1 Receptor
IHC	Immunohistochemistry
INR	International normalized ration
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous(ly)
LC	Leptomeningeal Carcinomatosis
LDK378	Ceritinib
LFT	Liver function test
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N/A	Not applicable
NSAIDs	Non-steroidal, anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
OERR	Overall extracranial response rate
OIRR	Overall intracranial response rate
ORR	Overall response rate
OS	Overall survival

[redacted]

OTC	Over the counter
[redacted]	[redacted]
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetics
PPS	Per-protocol set
PR	Partial response
PS	Performance Status
QD	quaque diem/once daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia formula
R Value	ALT/ALP in x ULN
Racc	Accumulation ratio
RANO	Response Assessment in Neuro-Oncology
RBC	Red blood cell
RD	Recommended dose
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Steering Committee
SD	Stable disease
SEC	Safety event categories
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI units	Standard international units
SRS	Stereotactic radiosurgery
SUSARs	Suspected unexpected serious adverse reactions
T1/2	Elimination half-life associated with the terminal slope (lambda_z) of a semilogarithmic concentration-time curve (time).
TKIs	Tyrosine kinase inhibitors
Tmax	The time to reach maximum plasma concentration
TTER	Time to extracranial response
TTIR	Time to intracranial response
TTR	Time to response
ULN	Upper limit of normal
VATS	Video-assisted thoracic surgery
VEGF-A	Vascular endothelial growth factor-A
Vss	Volume of distribution at steady state
WBC	White blood cells
WBRT	Whole brain radiation therapy
WHO	World Health Organization

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Biological samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q 21 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., before starting any of the study procedures described in the protocol)
Investigational drug	The drug 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 identifier number (consisting of the center number and a patient-specific number) assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study treatment	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any combination or control drug(s)
Study treatment discontinuation	Point/time when the patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled
Variable	A quantity subject to variation of values used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
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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Protocol summary

Protocol number	CLDK378A2205
Title	A phase II, multi-center, open-label, five-arm study to evaluate the efficacy and safety of oral ceritinib treatment for patients with ALK-Positive Non-Small Cell Lung Cancer metastatic to the brain and/or to leptomeninges
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This is a phase II, multi-center, open-label, five-arm study to evaluate the efficacy and safety of oral ceritinib treatment for patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges. Only patients whose tumors harbor ALK rearrangement will be enrolled in the study.
Primary Objective(s) and Key Secondary Objective	The primary objective is to evaluate the antitumor activity of ceritinib in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges based on whole body overall response rate (ORR), defined as the proportion of patients with a best overall confirmed response of complete response (CR) or partial response (PR) in the whole body as assessed per RECIST 1.1 by the investigator. The key secondary objective is to evaluate whole body Disease Control Rate (DCR) in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges based on investigator assessment per RECIST 1.1
Secondary Objectives	1. To evaluate intracranial tumor-response related endpoints as assessed by investigators and Blinded Independent Review Committee (BIRC) (using modified RECIST 1.1 criteria) 2. To evaluate extracranial tumor-response related endpoints as assessed by investigators and BIRC (using RECIST 1.1 criteria) 3. To evaluate whole body tumor-response related endpoints as assessed by investigators and BIRC (using RECIST 1.1 criteria) 4. To evaluate overall survival (OS) in this patient population 5. To evaluate safety in this patient population [redacted]
Study design	This is a phase II, multi-center, open-label, five-arm study in which the efficacy and safety of oral ceritinib treatment will be assessed in patients with NSCLC metastatic to the brain and/or to leptomeninges harboring a confirmed ALK rearrangement, using the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria). If documentation of ALK rearrangement as described above is not locally available, a test to confirm ALK rearrangement must be performed by a Novartis designated central laboratory. Patients must wait for the central laboratory result of the ALK rearrangement status before initiating treatment with ceritinib.
Population	Approximately 160 patients diagnosed with ALK-positive metastatic NSCLC (according to the 7th edition of the AJCC [American Joint Committee on Cancer] Cancer Staging Manual) and active lesions in the brain and/or diagnosed with leptomeningeal carcinomatosis will be included in the study, approximately 40 patients in Arm 1 and Arm 2, approximately 30 patients in Arms 3 and Arm 4, and approximately 20 patients in Arm 5. Additional patients may be enrolled in Arm 4 to i achieve approximately 60 patients in Arms 3 and 4 together (i.e. ALKi naïve patients), if enrollment rate in Arm 3 is slow. ● Arm 1 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously treated with radiation to the brain and with prior exposure to an ALKi. ● Arm 2 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously untreated with radiation to the brain but

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	with prior exposure to an ALKi. ● Arm 3 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously treated with radiation to the brain but with no prior exposure to an ALKi. ● Arm 4 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously untreated with radiation to the brain and with no prior exposure to an ALKi ● Arm 5 will include any patients with leptomeningeal carcinomatosis with or without evidence of active lesion at the baseline Gadolinium-enhanced brain MRI. Note: Previous treatment with ALK inhibitors other than crizotinib is not allowed in Arms 1, 2, and 5.
Inclusion criteria	**For all patients:** 1a. Histologically or cytologically confirmed diagnosis of metastatic NSCLC according to the 7th edition of the AJCC Cancer Staging Manual. In addition, the NSCLC must harbor an ALK rearrangement, as assessed using the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria). If documentation of ALK rearrangement as described above is not locally available, a test to confirm ALK rearrangement must be performed by a Novartis designated central laboratory. Patients must wait for the central laboratory result of the ALK rearrangement status before initiating treatment with ceritinib. 2a. Patients that require ALK rearrangement testing by a Novartis designated central laboratory must have a tumor tissue sample available as an archival sample (if possible obtained after the completion of the patient's last therapeutic regimen) or as a new biopsy. If that is not possible, any tumor biopsy obtained at or since the time of diagnosis can be used (a maximum of two years from biopsy excision is preferred). 3. At least one extracranial measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation. 4. Patient is 18 years of age or older at the time of informed consent. 5. Patients may or may not have neurological symptoms but must: ● Be able to swallow and retain oral medication. ● Be neurologically stable within at least 1 week prior to the first dose of study drug. Neurologically stable is defined as improved or stable neurological examination without increased doses of steroids to manage CNS symptoms within the last 5 days. 6a. Patients may have received prior chemotherapy, crizotinib (other ALK inhibitors are not allowed), biologic therapy or other investigational agents. Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v 4.03). Patients with any grade of alopecia are allowed to enter the study. • Patients who have been treated with chemotherapy, with biological therapy or other investigational agent must have discontinued the treatment at least 2 weeks (14 days) prior to starting study drug. In case last chemotherapy contains nitrosourea or mitomycin C, the treatment must be discontinued at least 6 weeks prior to the first dose of study drug. • Patients, if previously treated with crizotinib must discontinue treatment at least 1 week (7 days) prior to the first dose of study drug. 7a. Patient must meet the following laboratory values at the screening visit: • Absolute Neutrophil Count ≥ 1.5 x 10^9/L • Platelets ≥ 75 x 10^9/L • Hemoglobin (Hgb) ≥ 8 g/dL • Serum creatinine < 1.5 mg/dL and /or calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 30 mL/min • Total bilirubin ≤ 1.5 x 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 (AST) ≤ 3 x ULN, except for patients with liver metastasis, who are only included if AST ≤ 5 x ULN • Alanine transaminase (ALT) ≤ 3 x ULN, except for patients with liver metastasis, who are only included if ALT ≤ 5 x ULN • Alkaline phosphatase (ALP) ≤ 5.0 x ULN • Serum amylase ≤ 2 x ULN • Serum lipase ≤ ULN • Fasting plasma glucose ≤ 200 mg/dL (≤ 11.1 mmol/L) 8. Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements during screening: • Potassium • Magnesium • Phosphorus • Total calcium (corrected for serum albumin) 9. Patient has life expectancy ≥ 6 weeks. 10. Patient has a WHO performance status 0-2. 11. Patient has the ability to understand and provide signed informed consent. 12. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures. **Patients in Arm 1 to 4 must also meet the following inclusion criteria:** 13. Patients must have active brain metastases from NSCLC, confirmed by Gadolinium-enhanced MRI without concomitant leptomeningeal carcinomatosis. Dose of steroids must be stable for 5 days before the baseline brain MRI. Note: An active brain lesion is a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation). The following lesions are considered active: • A newly diagnosed brain metastasis in a patient who has never received treatment to the brain or in a patient with previously treated brain metastases. • A brain lesion previously treated with whole brain radiation will only be considered active when there is an unequivocal size increase in its solid component (cystic component of the lesion is not considered for progression determination) compared to the first available post-radiation radiological evaluation. • An enlarging brain lesion previously treated with SRS will only be considered active when the nature of the enlargement is clearly attributed to the tumoral component of the lesion and not to the radiation effect. **Patients in Arm 5 must also meet the following inclusion criteria:** 14. Patients must be diagnosed with leptomeningeal carcinomatosis. The diagnosis requires either documentation of the presence of malignant cells detected at the cytological examination of the cerebrospinal fluid or a serious suspicion of leptomeningeal carcinomatosis, supported by imaging findings typical of LC on the Gadolinium-enhanced MRI of the brain or spine (in this latter case, the determination of the presence of malignant cells in CSF cytology is strongly recommended).
Exclusion criteria	1. Patient with a history of treatment with ceritinib. Patient with known hypersensitivity to any of the excipients of ceritinib (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate). 2. Patients who need whole brain radiation to control the brain metastases. Patients will not be eligible unless treated brain lesions are progressive or new brain lesions are observed since the post whole brain radiation therapy MRI. 3. In case active brain lesions (single or not) require local treatment but other

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	active brain lesions do not and are not treated, patients will be excluded only if the local treatment (neurosurgical treatment or Stereotactic Radiosurgery) for the brain metastases is conducted within 2 weeks prior to starting study drug. Patients must have recovered from relevant toxicities related to these procedures to grade ≤ 1 (CTCAE v 4.03) prior to receiving the first dose of study drug. 4. Planning of any brain local treatment (including but not limited to surgery, stereotactic radiosurgery, whole brain radiation, intrathecal chemotherapy) following the administration of the first dose of study drug. 5. Patient who has received thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs) radiotherapy ≤ 2 weeks prior to starting the study treatment or has not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to the first dose of study drug is allowed. 6. Patient has had major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to the first dose of study drug or has not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can receive study treatment ≥1 week after the procedure. 7. Patient with a concurrent malignancy or history of a malignant disease other than NSCLC 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. 8. 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 anti-hypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to screening. • Ventricular 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). 9. Patient has impairment of GI function or GI disease that may significantly alter the absorption of ceritinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome). 10. 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 (Appendix 1): • Strong inhibitors or strong inducers of CYP3A4/5. • Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5 and/or CYP2C9. • Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes. 11. Patient is currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants. 12. Patient is receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated

[redacted]

	symptoms (non-CNS), dose must have been stabilized (or decreasing) for at least 5 days before first dose of study treatment. **Note:** Dose of steroids must be stable for 5 days before the baseline brain MRI. 13. Patient is receiving treatment with any enzyme-inducing anticonvulsant (Appendix 1) 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. 14. Patient is pregnant or nursing (lactating) woman. 15a. 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 study treatment. 16. Sexually active males 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. 17. Patient has other severe, acute, or chronic medical conditions including uncontrolled diabetes mellitus or psychiatric conditions 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. 18. Patient has history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention). 19. Patient has a history of pancreatitis or a history of increased amylase or lipase that was due to pancreatic disease. 20. Patient has been previously enrolled in the treatment phase of any ceritinib clinical study, regardless of which treatment group the patient was allocated or randomized to.
Investigational therapy	Ceritinib will be administered orally once daily at a dose of 750 mg (five 150 mg capsules) on a continuous dosing schedule. The treatment period will start on Cycle 1 Day 1.
Efficacy assessments	Complete tumor assessments including gadolinium enhanced brain MRI will be repeated at Week 8 (on Cycle 3 Day 1) and every 8 weeks (i.e. every 2 cycles) thereafter or earlier if clinically indicated. Tumor response will be evaluated starting from the first day of treatment with ceritinib until the time of disease progression according to RECIST 1.1 as determined by investigator, withdrawal of consent for further follow-up, loss to

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	follow-up or death. This schedule of tumor assessment must continue regardless of dose interruptions. In patients who discontinue treatment in the absence of progression, tumor assessments will continue every 8 weeks until progression of disease, withdrawal of consent for further follow-up, loss to follow-up or death. For patients presenting with baseline leptomeningeal carcinomatosis with documented malignant cells in the cerebrospinal fluid, CSF samples will be collected at a frequency determined by local clinical practice unless medically contra-indicated. Samples should be obtained from site of disease or initially positive cytology if possible. The investigator may determine if more frequent evaluations are needed in case of suspected disease progression and/or in accordance with local clinical practice. If there are any signs or radiologic or clinical neurological progression, a CSF will be collected if feasible. Clinical progression may be determined based on results of cytological or neurological evaluations. Gadolinium-enhanced brain MRI scans and all other imaging data collected at baseline and during the conduct of the study will be submitted to the designated imaging vendor for BIRC review. In this study, standard RECIST 1.1 will be used to evaluate the whole body (including intracranial and extracranial cancer lesions) response endpoints. Assessment of the overall response to treatment and other whole body response related endpoints will be conducted by investigators and BIRC. Additionally, the intracranial and the extracranial metastatic disease will be evaluated as two separate entities. Modified RECIST 1.1 and RANO for High Grade Glioma (Wen et al 2010) criteria will be used to determine intracranial tumor response based on brain target lesions, if applicable, any brain non-target lesions and any brain new lesions. RECIST 1.1 will be used to evaluate the extracranial tumor response but brain will be excluded from the evaluation.
Safety assessments	Adverse Events (AEs) including: • Serious AEs (SAEs) • Laboratory profiles • hematology • biochemistry • urinalysis • coagulation • pregnancy test (females) • Physical examination • Vital signs • Electrocardiograms (ECG) • WHO performance status
[redacted]	
Data analysis	The primary endpoint is the overall response rate (ORR), which is defined as the proportion of patients with a best overall confirmed response of CR or PR in the whole body, as assessed per RECIST 1.1 (Appendix 2) by the investigator. The key secondary endpoint is the Disease Control Rate (DCR), which is defined as the proportion of patients with a best overall response of CR, PR or SD in the whole body, as assessed per RECIST 1.1 by the investigator. Additionally, the following intracranial, extracranial and whole body (for lesions **inside and outside** the brain) tumor-response related endpoints (OIRR, IDCR, TTIR, DOIR, OERR, EDCR, TTER, DOER, TTR, DOR and PFS) will be assessed separately based on investigator assessment and BIRC assessment per RECIST 1.1. **Intracranial endpoints:** **Overall intracranial response rate (OIRR):** OIRR is calculated based on response assessments in the brain for patients having measurable brain metastases at baseline. The OIRR is defined as the proportion of patients with a

[redacted]

	best overall confirmed response of CR or PR in the brain as assessed per modified RECIST 1.1. OIRR will be estimated and the exact binomial 95% CI will be presented **Intracranial disease control rate (IDCR) at 8 and 16 weeks and overall:** IDCR is calculated based on response assessments in the brain for patients having evaluable (measurable or non-measurable) brain metastases at baseline. In what follows, CR, PR and SD are possible responses only for patients with measurable brain metastases at baseline, while non-CR/non-PD is a possible response only for patients without measurable brain metastases at baseline. • The IDCR at 8 and 16 weeks is defined as the proportion of patients with CR, PR, SD or non-CR/non-PD assessment in the brain at Week 8 and Week 16 intracranial tumor evaluations respectively. • IDCR overall is defined as the proportion of patients with a best overall response of CR, PR, SD or non-CR/non-PD in the brain, as assessed per modified RECIST 1.1. IDCR will be estimated and the exact binomial 95% CI will be presented. **Time to intracranial tumor response (TTIR):** TTIR is defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) in the brain as assessed per modified RECIST 1.1 criteria for patients with measurable brain metastases at baseline. The distribution function of TTIR will be estimated using the Kaplan-Meier method. The median TTIR along with 95% CI will be presented. **Duration of intracranial response (DOIR):** Among patients with measurable brain metastases at baseline and a confirmed response (PR or CR) in the brain per modified RECIST 1.1, DOIR is defined as the time from the first documented response (PR or CR) in the brain to the date of the first documented disease progression in the brain or death due to any cause. The distribution function of DOIR will be estimated using the Kaplan-Meier method. The median DOIR along with 95% CI will be presented. **Extracranial endpoints:** **Overall extracranial response rate (OERR):** OERR is defined as the proportion of patients with a best overall confirmed response of CR or PR outside of the brain, as assessed per RECIST 1.1. OERR will be estimated and the exact binomial 95% CI will be presented. **Extracranial disease control rate (EDCR) at 8 and 16 weeks and overall:** • EDCR at 8 and 16 weeks is defined as the proportion of patients with CR, PR or SD outside of the brain at Week 8 and Week 16 extracranial tumor evaluations, as assessed per RECIST 1.1. • EDCR overall is defined as the proportion of patients with a best overall response of CR, PR or SD outside of the brain as assessed per RECIST 1.1. EDCR will be estimated and the exact binomial 95% CI will be presented. **Time to extracranial tumor response (TTER):** TTER is defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) outside of the brain as assessed per RECIST 1.1 criteria. The distribution function of TTER will be estimated using the Kaplan-Meier method. The median TTER along with 95% CI will be presented. **Duration of extracranial response (DOER):** Among patients with a confirmed response (PR or CR) outside of the brain per RECIST 1.1, DOER is defined as the time from the first documented response (PR or CR) outside of the brain to the date of the first documented disease progression outside of the brain or death due to any cause. The distribution function of DOER will be estimated using the Kaplan-Meier method. The median DOER along with 95% CI will be presented. **Whole body endpoints:** **ORR by BIRC:** The evaluation of ORR will be repeated based on BIRC assessment. **DCR by BIRC:** The evaluation of DCR will be repeated based on BIRC assessment.

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	Time to tumor response (TTR): TTR is defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) in the whole body as assessed per RECIST 1.1 criteria. The distribution function of TTR will be estimated using the Kaplan-Meier method. The median TTR along with 95% CI will be presented. **Duration of response (DOR):** Among patients with a confirmed response (PR or CR) in the whole body per RECIST 1.1, DOR is defined as the time from the first documented response (PR or CR) to the date of the first documented disease progression or death due to any cause. The distribution function of DOR will be estimated using Kaplan-Meier method. The median DOR along with 95% CI will be presented. **Progression-free survival (PFS):** PFS is defined as the time from the date of the first dose of ceritinib to the date of the first documented disease progression in the whole body per RECIST 1.1 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 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 for any reason 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 for any reason 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. The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% CI will be presented. **Overall survival (OS):** OS time is defined as time from the date of first dose of ceritinib to the date of death due to any cause. OS time for patients who are alive at the end of the study or are lost to follow-up will be censored at the date of last contact. OS will be estimated using the Kaplan-Meier method. The median OS along with 95% CI will be presented. Kaplan-Meier curves will not be produced for Arm 5 alone if the number of patients enrolled in this arm is ≤ 10.
	[redacted]
	RANO exploratory objectives Exploratory analyses will be conducted to evaluate intracranial endpoints by investigator and BIRC including OIRR, TTIR, DOIR for patients with measurable brain metastases at baseline, and IDCR for all patients in Arms 1 to 4 with active brain lesion at baseline using Response Assessment in Neuro-Oncology (RANO) criteria for high grade gliomas (Appendix 3).
	[redacted]

[redacted]

	[redacted]
Key words	ALK, NSCLC, Ceritinib, brain metastasis

[redacted]

Amendment 6 (16-May-2018)

Amendment rationale

As of April 11, 2018, 156 patients have been enrolled in this study: 42 patients to Arm 1; 40 patients to Arm 2; 12 patients to Arm 3; 44 patients to Arm 4; and 18 patients to Arm 5. This study has been conducted as per protocol and the last patient was enrolled on August 31, 2017. At the time of this amendment all patients have already completed at least 24 weeks of treatment or discontinued treatment, thus the minimum patient follow-up needed to conduct the analyses for the primary and key secondary endpoints has been successfully achieved (this milestone has been reached on February 28, 2018). There are currently 45 ongoing patients still receiving ceritinib treatment in the study.

The end of the study had been planned once at least 75% of patients have died, have been lost to follow-up or have withdrawn consent for survival follow-up, following 24 weeks after last patient first treatment. Since the required follow-up for the primary and key secondary objectives have been reached and the roll over study will be made available for patients who are still ongoing on ceritinib, this amendment will allow ongoing patients benefiting from ceritinib to continue treatment with ceritinib by rolling over to this separate rollover study (and/or other options for continued treatment with ceritinib that are considered acceptable at the country level such as access to commercially available drug or managed access program). Therefore, the end of study LDK378A2205 will occur once all ongoing patients have been transitioned to the rollover study and/or other options for continued treatment or discontinued treatment before-hand.

The protocol originally defined that a primary analysis and study report would be performed after all patients have completed at least 24 weeks of treatment with ceritinib or have discontinued earlier and that the additional data collected thereafter would be reported in the final study report after the end of the study.

With this protocol amendment, a single final analysis and study report may be performed if the updated end of study criteria, as described above, is met before the primary analysis is conducted. If the end of the study criteria is not met by the time that the primary analysis is conducted, the additional follow up data will be reported in a final report, as initially planned.

[redacted]

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

List of changes to protocol:

- List of Abbreviations: DS&E (Safety & Epidemiology) is removed and replaced with the updated CMO&PS (Chief Medical Office & Patient Safety)
- Section 4.3: End of Study criteria is updated to reflect the available rollover protocol and/or other options for continued treatment with ceritinib. Updates for reporting data are made to account for if the EOS criteria is met before the primary analysis is conducted.
- Section 7.1.5: Withdrawal of consent language is updated to align with the update ICF Withdrawal of Consent language, which has been updated to incorporate and reflect the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements.
- Section 10: Updates for reporting data are made to account for if the EOS criteria is met before the primary analysis is conducted.
- Section 10.1.3: Per-Protocol Set is not applicable.
- Section 10.4.2: Clarified the patient arms to be used for analysis.
- Section 10.4.4: Supportive analyses is not applicable.
- Section 10.5.1: Clarified the patient arms to be used for analysis.
- Section 10.5.2: Clarified the patient arms to be used for analysis.

IRBs/IECs

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

[redacted]

Amendment 5 (31-May-2017)

Amendment rationale

As of May 31, 2017, 148 patients have been enrolled in this study: 42 patients to Arm 1; 40 patients to Arm 2; 10 patients to Arm 3; 38 patients to Arm 4; and 18 patients to Arm 5.

Patients with a diagnosis of Leptomeningeal carcinomatosis (LC) have a poor prognosis without treatment, with median overall survival (OS) of about ~1-1.5 months from diagnosis (Chamberlain 2010). Treatment with brain radiation may improve median overall survival (OS) to about 3 months (Morris et al 2012). Intrathecal chemotherapy for the treatment of NSCLC with LC is not clearly established (Park et al 2012) with a reported median OS of 5.5 months in patients with cytological response and 1.4 months for patients with no cytological response. EGFR-mutated NSCLC patients with LC have 5-6 months median OS if treated with EGFR TKi. There is no data available regarding the best treatment for ALK-positive NSCLC with LC disease in the current literature.

[redacted]

[redacted]

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

List of changes to protocol:

- [redacted]
- Table 6-3: Updated to include "recommendation" versus "mandatory" actions for each dose modification guideline. Updates to bradycardia range and clarification for the use of QTcF when evaluating QT prolongation, as QTcF is used to assess eligibility.
- Section 6.3.4: Minor updates to guidelines for the follow up of laboratory liver and pancreatic abnormalities sections by including R values to asses cholestatic versus hepatoceullar versus mixed livery injury.
- Section: 8.2: Update of SAE Reporting guidelines to specify reporting for signing of molecular pre-screening ICF versus main study ICF. Also includes clarification of the reporting period for follow-up SAE information. The DS&E is updated to the CMO&PS department.
- [redacted]
- [redacted]
- Section 11.5: Updated to outline the Novartis standards for publication of study protocol and results

IRBs/IECs

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.

[redacted]

Amendment 4 (22-Aug-2016)

Amendment rationale

As of Aug 22, 2016, 117 patients have been enrolled in this study: 34 patients to Arm 1; 38 patients to Arm 2; 7 patients to Arm 3; 23 patients to Arm 4; and 15 patients to Arm 5.

The purpose of this amendment is:

- To increase the sample size for Arms 1 and 2 to ~40 patients each in order to increase the robustness of the efficacy data from Arms 1 and 2 i.e. in the post crizotinib patient population. An increase of 20 patients (i.e. from 60 to 80 patients) in Arms 1 and 2 will enable the lower bound of the 95% CI of whole body ORR to be 48% which is clinically meaningful, if the observed whole body ORR is 60% (with 60 patients the lower bound for the 95% CI for ORR was 46.5%). Moreover, the addition of 20 patients in Arms 1 and 2 will allow this trial to have an adequate number of patients (~50) with measurable brain metastases in prior crizotinib treated group to assess the intracranial response rate.
- To increase the sample size for Arm 5 to ~20 patients to increase the robustness of efficacy data in patients with leptomeningeal carcinomatosis.
- To allow for additional patients enrollment in Arm 4 in order to achieve approximately 60 patients in Arms 3 and 4 together (i.e. ALKi naïve patients) if enrollment rate in Arm 3 is slow. This will increase the robustness of the efficacy data from Arms 3 and 4 (i.e. in ALKi naïve patient population).
- To allow for one early analysis CSR that will included data from appropriate study arms that have finished enrollment much earlier than other arms due to differential recruitment rate among the five study arms. The early primary analysis will be performed after enrollment in those arms is complete and all treated patients in those arms have been followed for at least 24 weeks or discontinued treatment.
- To analyze the secondary endpoints of IDCR (intracranial disease control rate) and EDCR (extracranial disease control rate) at 8 and 16 weeks (as opposed to 24) in order to characterize the IDCR and EDCR at early tumor assessment time points (1st and 2nd tumor assessments) and reduce the impact of early discontinuation of patients due to reasons other than intracranial/extracranial disease progression.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

List of changes to protocol:

- Section 1.2.1: Zykadia is updated with the registered ® symbol.
- Table 3-1: Secondary objective updated to clarify study population to be evaluated. Vital signs are added to endpoint analyses. IDCR and EDCR updated to 8 and 16 weeks.
- Figure 4-1: Updated to N~40 for Arm 1 and Arm 2, and N~20 for Arm 5.
- Section 4.1.1: The patient sample size for the study and each arm is updated and the study targets for patients with measurable brain metastases are updated.

[redacted]

- Section 4.1.2: Reference to additional sentence clarifying ceritinib continuation after PD both intracranially and extracranially is included.
- Section 4.1.2.2: Sentence added to clarify ceritinib continuation after PD both intracranially and extracranially.
- [redacted]
- Section 5.1: The patient population is updated to approximately 160.
- Section 6.1.3: Sentence added to clarify ceritinib continuation after PD both intracranially and extracranially.
- Section 6.3.4.2: Typo corrected to "liver" function tests.
- Section 6.4.1.5: Ceritinib should be held in any situation when radiotherapy or surgery is required.
- Section 6.4.2.1: Included "and palliative surgery" in reference to Section 6.4.1.5 Palliative radiosurgery and surgery.
- Section 7.1.4.1: Sentence added to clarify ceritinib continuation after PD both intracranially and extracranially.
- Section 7.2.1.3: Sentence added to clarify ceritinib continuation after PD both intracranially and extracranially.
- [redacted]
- [redacted] analyzed for those arms included in the early primary analysis. A primary analysis of all study arms 1-5 and the subsequent report is clarified to not include data from an early analysis. [redacted]
- Section 10.4.2: ORR statistical analysis is clarified.
- Section 10.4.3: RAP is clarified to RAP document.
- [redacted]
- Section 10.5.1: Key secondary objective(s) is updated to clarify the data analyzed for secondary efficacy objectives.
- Section 10.5.2: Other secondary efficacy objectives are clarified for data which will be used for analysis.
- Section 10.5.2: IDCR at 24 weeks is updated to IDCR 8 and 16 weeks. EDCR at 24 weeks is updated to EDCR 8 and 16 weeks.
- Section 10.5.3.1: Safety analysis will be presented by study arm and for all patients.
- Section 10.5.3.4: RAP is clarified to RAP document.

[redacted]

- Section 10.8: Sample size calculation is updated to N=160 and updated per arm. Arm 4 may enroll additional patients in order to achieve approximately N=60 in Arms 3 + 4.
- Table 10-1: Calculations are updated for N=140 in Arms 1-4 and includes analysis of Arms 1 and 2. N is updated to 40 for each of Arms 1 or 2.
- Section 10.9: Update to N=140 in Arms 1-4 and subsequent evaluation for treatment groups.

[redacted]

- Table 10-3: Include data for groups Arms 1-4, Arms 1+2, Arms 3+4.

[redacted]

IRBs/IECs

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The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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 protocol amendment.

[redacted]

Amendment 3

Amendment Rationale

As of November 2, 2015, 21 patients have been enrolled in this study.

- The purpose of this amendment is to revise protocol language regarding the requirement to confirm ALK rearrangement at the Novartis designated central laboratory before initiating treatment with ceritinib.
  - Confirmation of ALK rearrangement by the Novartis designated central laboratory before initiating treatment with ceritinib will only be required if there is no locally available documentation of ALK rearrangement (ALK positive status) with the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbot Molecular Inc.) test and scoring algorithm (including positivity criteria).
  - If documentation of ALK rearrangement as described above is not locally available at the site, a test to confirm ALK rearrangement must be performed by the Novartis designated central laboratory and patients must wait for the central laboratory result of the ALK rearrangement status before initiating treatment with ceritinib.
- This amendment also clarifies the eligibility criteria for enrollment of patients with prior exposure to ALK inhibitors in Arm 1, Arm 2, and Arm 5 to only allow enrollment of patients that have been treated with prior crizotinib. Patients previously treated with ALK inhibitors other than crizotinib are not permitted into the study. The change is made to ensure homogeneity in the group of patients with prior ALK-inhibitor exposure given the small sample size of each cohort. This patient population is also consistent with the currently approved indication for Zykadia (ceritinib) in many countries.
- The amendment also provides follow up evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases in order to optimize patient safety.
- Other changes were also implemented in this amendment:
  - Exclusion criteria for contraception use is being updated to reflect the current guidance.
  - Dose guidance modification for QTc text was updated to provide clarification on monitoring procedures.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- List of Abbreviations: updated to include DILI, R Value, eSAE and to change abbreviation of RAP to SAP
- Table 2-1, Section 2.2, Section 4.1 and Figure 4-1: added footnote to restrict previous ALK inhibitors to only crizotinib to align with the currently approved indication based on regulatory feedback

[redacted]

- Section 4.1.1, Section 7.1.1, Section 7.1.1.1, and Section 7.1.2: updated to clarify requirement of ALK rearrangement testing
- Section 4.1.2 and Section 7.1.3: corrected language to remove erroneous use of the word "equivocal"
- Section 5.2: inclusion criteria #1 has been replaced by inclusion criteria #1a to clarify requirement of ALK rearrangement testing
- Section 5.2: inclusion criteria #2 has been replaced by inclusion criteria #2a to clarify requirement of tumor tissue sample in accordance with ALK rearrangement testing
- Section 5.2: inclusion criteria #6 has been replaced by inclusion criteria #6a to restrict previous ALK inhibitors to only crizotinib to align with the currently approved indication
- Section 5.2: inclusion criteria #7 has been replaced by inclusion criteria #7a and updated to correct typographical errors from the prior amendment regarding serum amylase laboratory value
- Section 5.3: exclusion criteria #15 has been replaced by exclusion criteria #15a to update language regarding contraception
- Table 6-3: table updated to fix a typographical error and further clarify QTc monitoring procedure for Grade 3 QT interval
- Table 6-4: updated to elaborate on follow-up evaluations for hepatic toxicities
- Section 6.3.4.2: updated language regarding hepatic toxicity evaluations and guidelines for potential Drug Induced Liver Injury (DILI) cases to reflect currently available safety data
- Section 6.4.1.5: updated language to clarify ceritinib use during palliative surgical intervention
- Table 7-1: updated footnote to clarify requirement of ALK rearrangement testing and required activities associated with pre-screening and screening phase
- Section 7.1.2: updated language to clarify that investigators may repeat laboratory assessments before dosing if deemed clinically necessary and/or per institution policies
- Section 7.2.3.2: updated language to allow patients to forgo CSF collection if deemed to be an unacceptable burden for patients
- [redacted]
- Section 7.2.4: updated to further align with inclusion criteria #14 and to clarify requirements for leptomeningeal carcinomatosis (LC) diagnosis
- Section 7.2.5.2: updated to be consistent with protocol language
- Section 8.1.1: paragraph added to clarify Adverse Event reporting for patients who have signed molecular pre-screening ICF in order to be consistent with language in Section 7.1.2.2 and added language to clarify reporting requirements
- Section 8.2.2: updated language for guidance of reporting of SAEs
- Section 10.1.3 and Section 10.1.5: updated to align with the new Reporting and Analysis Process

[redacted]

- Table 14-4: Added medications to reflect updated list of prohibited medications causing QTc prolongation

IRB/IEC

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.

The changes herein affect the Informed Consent forms. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Summary of previous amendment(s)

Amendment 2

Amendment Rationale

The primary purpose of this amendment is to revise protocol sections based on additional clarifications related to safety and practical operationalization of the study, based on feedback from participating countries and further review.

In addition, updates to the protocol have been made based on currently available safety data. Pancreatic enzyme elevations (lipase and/or amylase) occur in patients treated with ceritinib. Clinical data suggest that a small proportion (<1%) of patients treated with ceritinib can develop clinical pancreatitis, and the causal role of ceritinib in these cases cannot be excluded. Due to this finding, the protocol has been amended to include relevant exclusion criteria, additional dose modification and follow up monitoring language for patients who may experience this safety finding.

Dose Modification language was further updated to provide additional guidance for monitoring patients with QTcF interval prolongation greater than 500 ms [redacted]

Updated language for patient discontinuation was added to the protocol and to the Informed Consent Forms (ICF) to provide guidance on how to effectively manage patients who discontinue from the clinical trial.

Updated safety data was added to the protocol and to the ICF to be consistent with the Investigator's Brochure Edition 7 (released on 12-Jun-2014). In addition, adverse events of special interest will be monitored for ceritinib.

An evaluation of the anticipated benefits and risks has been included in the protocol to comply with EU clinical trial regulations.

[redacted]

Additional minor edits have been made to protocol language for clarification as well as to maintain consistency and harmonization amongst other LDK378 global program protocols.

Changes to the Protocol

Main changes include:

[redacted]

- Section 1.1: edits and/or additional information to clarify text and provide updated background information for study, based on pre-clinical and non-clinical data
- Section 1.2: additional information provided based on updated clinical experience, related to safety and pharmacokinetic data from clinical studies
- Section 1.3: risk/benefits rationale added to comply with EU clinical trial regulations
- [redacted]
- Sections 4.1.1 and 7.1.2; Table 7-1: modified language to allow greater flexibility in the time between pre-screening and screening for those patients who have locally available source documentation with confirmed ALK positive status by the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria); updated to increase operational flexibility at sites and minimize burden for patients during those two study phases
- Section 4.1.2: further clarified terminology of disease progression when 'equivocal' per definitions of RECIST and updated timing of tumor assessment, based on regional feedback from participating countries
- Sections 4.3 and 10: included language to distinguish primary analyses and associated clinical study report (CSR) that will be produced from that of CSR compiled at the end of the study
- Section 4.3: updated section to replace terminology in reference to a rollover study
- Section 4.4: updated terminology to match glossary and updated language with regard to patients who discontinue clinical trial
- Section 5.2: inclusion criteria #2 and throughout protocol sections, where screening (Sections 4.1.1.1 and 7.1.2) and tumor sample requirements (7.1.1.1) are referenced, added language to further clarify preferred timing of archival samples
- Section 5.2: inclusion criteria #14 updated requirement of documentation to supplement diagnosis of leptomeningeal carcinomatosis based on feedback from participating study site regarding the presence of typical signs of LC at the brain/spine MRI that are sufficient to establish a diagnosis since CSF cytology is not systematically positive
- Section 5.3: exclusion criteria #8 to clarify that the threshold of QTcF >470 ms at screening visit should be based on the mean of the (triplicate) scheduled ECGs per Section 7.2.2.7
- Section 5.3: exclusion criteria #15 and 16 modified to remove incorrect wording of "reference chemotherapy" in respective criteria, as only reference to ceritinib is applicable this study
- Section 5.3: exclusion criteria #19 added to exclude patients with history of pancreatitis or a history of increased amylase or lipase that was due to pancreatic disease
- Section 5.3: exclusion criteria #20 added to exclude patients who have been previously enrolled in a ceritinib clinical study to prevent the same individual from enrolling in multiple studies within the LDK378 global program
- Table 6-3: table was updated to provide guidance on dose modifications related to pancreatic laboratory abnormalities (amylase and lipase), creatinine, as well as for related changes on electrocardiograms

[redacted]

- Table 6-4: table updated to include toxicity guidance for ≥ grade 3 amylase and lipase
- Section 7.1.1.1: removed sentence regarding timeframe of ICF signature as the pre-screening and screening phase is described in Table 7-1 and confirmation of ALK status from the Novartis-designated central laboratory is required to proceed.
- Section 7.1.2.2: corrected language to omit the word "randomization" and replace with "enrollment" to the next study phase
- Section 7.1.2.3: updated to reflect that demographics and confirmation of ALK status occurs at pre-screening
- Section 7.1.4.1; Section 7.1.5; Section 7.1.7: updated to provide language to effectively manage patients who discontinue clinical trial
- Section 7.2.1: includes additional information collected to supplement imaging review process, involving CRO and BIRC
- Section 7.2.2.6 and Section 7.2.2.6.3: added to allow flexibility and provide instruction based on site feedback
- Table 7-4: table updated to include missing laboratory collection of lipase
- Section 7.2.3.2: added based on operationalization feedback from participating country
- Section 7.2.3.2 and 7.2.4: added language regarding the need to rule out any applicable medical condition that would prevent a planned CSF sampling procedure
- Section 7.2.3.3: updated language for use of new methods to measure ceritinib plasma and CSF samples in a more timely manner and at a possibly lower level, respectively
- Section 7.2.4: updated for requirement of documentation to supplement diagnosis of leptomeningeal carcinomatosis
- Section 7.2.5.1, Table 7-8: correction made for consistency with protocol and related Informed Consent Forms

[redacted]

Other changes include:

- Glossary of terms: biological sample and withdrawal of consent were added to the table. Other terms and definitions not used or not applicable in this study were removed
- Table 3-1: definition of modified RECIST provided as a footnote for clarity and reference to this table
- Table 7-1: corrected formatting throughout table and removed typographical error that included cytology when not applicable in this study during screening phase
- References: modified accordingly based on new information provided in protocol and updated typographical errors

IRB/IEC

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.

[redacted]

The changes herein affect the Informed Consent forms. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1

Amendment Rationale

The purpose of this amendment is to revise protocol sections and provide additional clarifications on study procedures related to ALK testing and BIRC review.

Main changes include:

- Revision of Inclusion criteria #1 and addition of a new inclusion criteria #2 to clarify the need for central ALK rearrangement status determination for all patients at a Novartis designated laboratory before initiation of treatment with ceritinib.
- Revision of Inclusion criteria #2: At least one extracranial measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation. Note: Enrollment of patients with only non-measurable brain metastases may be closed in one or more arms if it is determined that the target for patients with measurable brain metastases across study arms will not be met.
- The measurability of brain metastases will be confirmed by BIRC per RECIST 1.1 on an ongoing basis to target a similar number of patients with measurable brain metastases in the subgroup of patients with prior radiotherapy to the brain (combined arms 1 and 3) and the subgroup of patients with no prior radiotherapy to the brain (combined arms 2 and 4). Enrollment of patients with only non-measurable brain metastases (even in the presence of extracranial measurable lesions) may be closed in one or more arms if it is determined that the above target for patients with measurable brain metastases will not be met.

Other changes include:

- Revision of slice thickness requirements for brain Gadolinium-enhanced MRI.
- In addition, editorial changes and text corrections were made for clarification, where required.
- Removal of start of new anti-cancer therapy as a reason for stopping tumor assessments to allow for sensitivity analysis of PFS in ITT population.

Changes to the Protocol

- Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.
- The following sections to the protocol were changed:
- List of abbreviations: editorial updates.
- Synopsis: clarifications on the data analysis section regarding primary and secondary endpoints.
- Section 4.1.1, Section 7.2.1.3 and Section 8.8.: addition/clarification of text “The measurability of brain metastases will be confirmed by BIRC per RECIST 1.1 on an

[redacted]

ongoing basis to target a similar number of patients with measurable brain metastases in the subgroup of patients with prior radiotherapy to the brain (combined arms 1 and 3) and the subgroup of patients with no prior radiotherapy to the brain (combined arms 2 and 4). Enrollment of patients with only non-measurable brain metastases (even in the presence of extracranial measurable lesions) may be closed in one or more arms if it is determined that the above target for patients with measurable brain metastases will not be met".

- Section 4.1.1, Section 7.1.1 and Section 7.1.2: clarification of study procedures to align with changes made to inclusion criteria #1 and #2.
- Section 4.1.2.1, Section 7.1.4.1 and Section 7.1.5.2: removal of start of new anti-cancer therapy as a reason for stopping tumor assessments to allow for sensitivity analysis of PFS in ITT population.
- Section 5.2: revision of Inclusion criteria #1 and addition of new inclusion criteria #2 to clarify the need for central ALK rearrangement status determination for all patients at a Novartis designated laboratory before initiation of treatment with ceritinib.
- Section 5.2: revision of Inclusion criteria #2: At least one extracranial measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation. Note: Enrollment of patients with only non-measurable brain metastases may be closed in one or more arms if it is determined that the target for patients with measurable brain metastases across study arms will not be met.
- Section 5.3: revision of Exclusion criteria #8 to remove "(as mean of triplicate ECGs)" clarifying procedures.
- Table 6-3: updated guidance for Grade 3 QTc interval prolongation.
- Section 6.4.1.2: clarification of bisphosphonate treatment guidance.
- Section 6.4.2.6: clarification of language on medications that are CYP2C9 and CYP3A4/5 substrates with narrow therapeutic index.

[redacted]

- Section 7.1.1 and Section 7.1.2: Clarifications on the molecular screening and screening procedures regarding tumor requirements and request for ALK rearrangement status determination by Novartis designated central laboratory.
- Section 7.1.2: clarification under the screening section was added: the cardiac eligibility criteria should be assessed with the central ECG report. Also, updated language to allow re-screenings.
- Section 7.1.2.2: revised language to clarify information to be collected for screening failures.
- Section 7.2.1.1: revision of slice thickness requirements for brain Gadolinium-enhanced MRI: if technically possible slice thickness should preferably be 1mm, but it should not exceed 5 mm.
- Section 7.2.2.6, Section 7.2.3.1 and 7.2.5.2: remove reference to laboratory manual.

[redacted]

- Table 7-8: updated to reflect new tumor sample requirements.
- Section 9.4: statement on diary data removed as it is not applicable in this study.
- Section 13: updated reference list.
- Appendix Table 14-2: list of medication to be used with caution updated and removal of ritonavir, clarithromycin and telithromycin.
- Editorial and typographical changes throughout the document as required.

IRB/IEC

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.

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Locally advanced or metastatic non-small cell lung cancer (NSCLC)

Lung cancer has been among the most common cancers in the world for several decades. Worldwide, lung cancer occurred in approximately 1.8 million patients in 2012 and caused an estimated 1.6 million deaths. (Brambilla et al 2014). In 2012, approximately 160,000 and 262,000 deaths, respectively, due to lung cancer were expected in the United States (US; Siegel et al 2012) and in the European Union (EU; Malvezzi et al 2012).

The World Health Organization (WHO) divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: NSCLC and small cell lung cancer. NSCLC accounts for more than 85% of all lung cancer cases and includes 2 major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types); and (2) squamous cell (epidermoid) carcinoma. Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer seen in the US and is also the most frequently occurring cell type in nonsmokers (NCCN Guidelines v13 2014).

Cigarette smoking remains the most important risk factor for lung cancer, although approximately 15% of all lung cancers are diagnosed in patients who never smoked.The high mortality rate of lung cancer could be explained in an advanced stage for most cases; only 25-30% of new NSCLC cases are diagnosed with localized disease that is potentially curable with surgery (Nguyen et al 2012). The majority of patients is diagnosed with locally advanced or metastatic disease, for which surgery is not indicated.

Brain metastases (BM) are a common complication of patients with NSCLC. Ten to 35% of the patients newly diagnosed with NSCLC presents with synchronous BM (Preusser 2012, Olak 2000). One third of these patients are asymptomatic (Hendriks et al 2013). The incidence of synchronous BM may have increased in recent years as result of more aggressive staging procedures as recommend by guidelines and advances in neuro-imaging techniques.

If not present at the time of the initial presentation of the NSCLC disease, BM will develop during the length of the disease. It is estimated that 40 to 50% of all patients with NSCLC will develop BM at any stage of the treatment of their disease. This incidence is also increasing the last years resulting for the use of more effective systemic treatments translating into prolonged survival (Wen et al 1999). BM treatments are usually palliative with the intent to control the brain disease, which at best is achievable for a brief duration. Treatment options are limited and comprise of whole brain radiation therapy (WBRT) leading to a modest overall survival benefit. Additional local treatment such as neurosurgery or stereotactic radiosurgery (SRS) may contribute to longer brain disease control. (Bowden 2013, Patil 2012, Shaw 2013)

The role of systemic therapies in the treatment of BM remains unclear to date. For decades, systemic chemotherapies were believed to be of limited benefit. The brain, protected by a

[redacted]

blood-brain-barrier (BBB) with low permeability to large molecules, is usually seen as a pharmacologic sanctuary.

Patients with disease metastatic to the brain were generally excluded from most large studies evaluating chemotherapeutic agents as treatment for advanced or metastatic NSCLC. With the exception of platinum-based chemotherapy, most chemotherapeutic agents evaluated in small studies reveal modest activity on NSCLC brain lesions (response rate ranging from 5 to 27%) (Vogelbaum 2010, Moscetti 2007, Barlesi 2011) due to insufficient drug penetration through the BBB, even if the BBB is potentially disrupted by the brain metastases.

Despite emerging data suggesting that systemic treatment may be considered a treatment option for patients with NSCLC metastatic to the brain, the current National Comprehensive Cancer Network (NCCN) Guidelines for the treatment of NSCLC patients with BM, still recommend localized treatment of the brain disease prior to initiating systemic treatment for advanced incurable patients (NCCN Guidelines v13 2014). Whole Brain Radiation Therapy (WBRT) is indicated in case of diffuse BM, without restriction, if the patient is neurologically asymptomatic. In case of solitary BM, Stereotactic Radiosurgery (SRS) followed or not by WBRT or neurosurgery always followed by WBRT are recommended prior to the start of platinum-based combination chemotherapy. Platinum-doublet chemotherapy (cisplatin or carboplatin in combination with other chemotherapy agents, with or without bevacizumab) is standard first line treatment for patients with a Performance Status (PS) of 0 and 1, or for selected patients with a PS of 2 with locally advanced or metastatic NSCLC, unless the lung cancer has a known "druggable" (molecularly targetable) gene mutation or aberration rendering these patients candidates for first line targeted therapy (as discussed below) instead of chemotherapy. Although chemotherapy has led to clinical improvements in patients with locally advanced or metastatic NSCLC, the outcome of treatment in the first-line setting remains poor, with median progression-free survival (PFS) and overall survival (OS) of 5-7 months and 10-16 months, respectively (Scagliotti 2008, Ciuleanu 2009, Ettinger 2010, Paz-Ares 2012).

Overall, current treatments are not considered satisfactory for most NSCLC patients with BM and the prognosis continues to be poor, with a 5-year OS rate of only 15% (Nguyen et al 2012). In particular, the prognosis for patients presenting with advanced, incurable disease is dismal, with a 5-year OS rate of 3.7% (Howlader et al 2009).

1.1.2 Targeted therapies in NSCLC

During the last few years, improved knowledge of NSCLC biology has led to the identification of molecular events crucial for malignant transformation and cancer cell survival and "molecular subsets" of NSCLC patients who may be candidates for targeted therapy. These aberrant molecular events are critical oncogenic drivers and represent potential therapeutic targets (Gettinger et al 2011). As a result, new targeted treatment options have been developed and are evolving. Erlotinib and gefitinib, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), have been approved for the treatment of NSCLC. In particular, EGFR TKIs represent a new paradigm in the treatment of NSCLC. Activating mutations in EGFR are found in 10-15% of Caucasian and 30-40% of Asian NSCLC patients and are associated with a higher response to EGFR TKIs (Ettinger et al 2010). Multiple large randomized clinical trials have demonstrated that patients harboring activating EGFR

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mutations benefit more from EGFR TKIs than from standard chemotherapy in terms of overall response rate (ORR), PFS, toxicity profile, and quality of life (Ettinger 2010, Besse 2013).

Given their low molecular weight, it is assumed that these agents may penetrate and reach brain metastases more readily and may be more effective than chemotherapies. Small studies reported clinical activity of EGFR TKIs in brain metastases of NSCLC patients harboring activating mutation of EGFR (Karachaliou 2013, Wu 2013). These observations open the way to reevaluate the role of systemic treatment for BM when highly effective drugs have a relatively low molecular weight.

1.1.3 ALK rearranged (ALK-positive, ALK+) NSCLC

The discovery of anaplastic lymphoma kinase (ALK) gene rearrangement in NSCLC in 2007 (Soda et al 2007) represents another important milestone in the era of molecular targeted therapy in NSCLC.

ALK was first identified as a chromosome translocation-produced protein fusion in the majority of anaplastic large cell lymphomas (ALCL). When fused to other proteins, ALK becomes constitutively active, leading to increased catalytic kinase function, signal-transduction activity, and oncogenic function. Other fusion partners of ALK have been described (e.g., KIF5B, TFG, KLC1 and PTPN3), but these are less common than EML4 (Kruczynski et al 2012). Preclinical experiments have shown that the various ALK fusion partners mediate ligand-independent dimerization/oligomerization of ALK resulting in constitutive kinase activity and in potent oncogenic activity both *in vitro* and *in vivo*. This activity can be effectively blocked by small-molecule inhibitors that target ALK.

Expression of EML4-ALK, a new fusion protein between ALK and the echinoderm microtubule-associated protein-like 4 (EML4) gene, in transgenic mice has been shown to induce tumor formation, suggesting the therapeutic potential of targeting the EML4-ALK fusion protein in NSCLC (Soda et al 2007). The frequency of EML4-ALK rearrangement in patients with NSCLC is relatively low; it is present in approximately 2-8% of tumors tested (Scagliotti 2012; Takeuchi 2009; Soda 2007; Takeuchi 2009; Soda 2007). However, considering the high incidence of lung cancer, this small percentage translates into about 10,000 patients in the US alone (Kwak et al 2010).

Patients with ALK-rearranged NSCLC are similar to those with EGFR mutations (i.e., adenocarcinoma, nonsmokers or former smokers), up to 30% of smokers or former smokers has been included in the pivotal phase 3 study evaluating crizotinib after first line of treatment for ALK-rearranged NSCLC (Shaw et al 2013) except they are often younger. In addition, ALK rearrangements are found in patients with adenocarcinoma but not usually found in squamous cell or large cell carcinoma (Shaw et al 2009). ALK rearrangements and other oncogenic drivers such as mutant EGFR and oncogenic RAS are most of the time mutually exclusive, consistent with the notion that ALK rearrangement defines a unique molecular subset of NSCLC.

ALK-rearrangement may predispose patients to develop BM but current literature remains controversial (Doebele 2012, Yang 2012, Kang 2013). It is interesting to note that ALK rearrangement in NSCLC is mostly observed in adenocarcinoma (90%) and large cell

[redacted]

carcinoma (10%) histologic subtypes. The adenocarcinoma subtype is known to be associated with an increased risk of developing BM (Saha 2013, Sanchez 2009). Shi et al (2006) reported a 58% incidence of BM in patients with adenocarcinoma of the lung and in 17.7% of patients with a large call carcinoma of the lung.

ALK rearrangements serve as a key strong oncogenic driver for NSCLC and represent a critical therapeutic target susceptible to targeted ALK kinase inhibition.

Crizotinib, an orally available small-molecule inhibitor of ALK and MET tyrosine kinases, is the first tyrosine kinase inhibitor to target ALK to have demonstrated a clinical activity and to be approved in the US as treatment of metastatic ALK-positive NSCLC. Advanced or metastatic ALK-positive NSCLC patients, after failure to a prior platinum-based chemotherapy, experienced a higher response rate (RR) to crizotinib (RR=65%;95%CI:58-72) compared to chemotherapy (RR=20%; 95CI:14-26) and a longer progression free survival (PFS) if treated with crizotinib compared with second-line chemotherapy (7.7 months versus 3.0 months, HR=0.49; 95% CI, 0.37 – 0.64) (Shaw et al 2013).

The most frequent adverse events (AEs) with crizotinib treatment are visual disorders, occurring in approximately 60% of patients (Shaw et al 2013). Other common toxicities include gastro-intestinal (GI) disorders (diarrhea 60%, nausea 55%, vomiting 47%), elevations of liver enzymes (38%), edema (31%), fatigue (27%), upper respiratory infection (26%), dysgeusia (26%), dizziness (22%), dyspnea (13%), skin rash (9%) and alopecia (8%). Three AEs warranted warning and precautions in the package insert (pneumonitis, hepatic laboratory abnormalities and QT prolongation). In addition, rapid onset of hypogonadism in the majority of male patients taking crizotinib has been reported (Weickhardt et al 2012).

While crizotinib has impressive activity in patients with ALK rearranged NSCLC, these cancers invariably progress, typically within 1 year, with the development of resistance to crizotinib (Kwak et al 2010). Otterson et al (2012) reported CNS being the first site of progression in 46% of patients with ALK-positive NSCLC patients treated with crizotinib. Crizotinib, despite a 450 Dalton molecular weight has a low penetration to the brain. Costa et al (2012) evaluated a patient who developed isolated BM during crizotinib treatment. The crizotinib CSF concentration was measured at 0.616 ng/mL compared to 237 ng/mL in the plasma. This case indicates that crizotinib does not penetrate through the blood-brain barrier or penetrates insufficiently to prevent the onset of brain metastases.

Crizotinib may have clinical activity when used to treat ALK-positive NSCLC patients metastatic to the brain. Out of the 347 patients included in the pivotal phase III study PROFILE 1007, 120 patients (35%) presented with untreated asymptomatic or treated and stable brain metastases at baseline. They were equally distributed across study arm (60 were randomized to the chemotherapy arm and the other 60 to the crizotinib arm. (Shaw et al 2013). PFS was evaluated in subgroups of patients with or without BM at baseline. Hazard ratio still favored crizotinib compared to second-line chemotherapy in patients with BM (HR=0.67; 95%CI: 0.44 – 1.03). The comparison to the result for the subgroup of crizotinib-treated patients without BM (HR=0.43; 95% CI, 0.30 – 0.60) suggest that crizotinib efficacy is better in patients without BM than those with BM.

Crino et al. (ECC 2013 – Abst#3413) reviewed the intracranial activity of crizotinib when administered as treatment for metastatic ALK-positive NSCLC patients. Two-hundred-

[redacted]

seventy-five out of 888 patients treated with crizotinib were selected for this retrospective analysis because they were included in the PROFILE 1005 and 1007 studies with brain metastases. Intracranial endpoints were defined as including only intracranial sites of disease and systemic endpoints, as including only extracranial sites of disease. The intracranial and extracranial response was evaluated using RECIST 1.1.

The reported Overall Intracranial Response Rate (CR+PR) in a subgroup of 109 patients with untreated BM was 7% (95%CI: 3-14) compared to an extracranial Response Rate of 53% (95% CI: 43-63). Out of these 109 patients, 22 presented with BM qualifying for target lesion following RECIST 1.1. The OIRR in these 22 patients was 18% (95% CI: 4-40). In the subgroup of 109 patients with untreated BM at baseline, the intracranial disease control rate at 12 weeks was reported at 56% (95% CI: 46-66) and the median duration of intracranial response was 26.4 weeks (95% CI: 4.9 to 59.3 weeks). The systemic disease control rate at 12 weeks in this group was reported at 63% (95% CI: 54-72) and the median duration of systemic response was 47.9 weeks (95% CI: 5.3 to 55.0 weeks).

Leptomeningeal carcinomatosis (LC) is a rare devastating disease resulting from the seeding of malignant cells to the leptomeninges and cerebrospinal fluid (CSF). LC is observed in approximately 5% of the patients diagnosed with metastatic NSCLC (Chamberlain 2010). The incidence of LC in ALK-positive NSCLC may be around 5 to 6% (Gainor et al 2013). Median survival without treatment is about 4-6 weeks and about 4 months with the available treatments (whole brain radiation therapy and intrathecal chemotherapy) (Lee 2013, Palma 2013). The role of systemic treatment for LC has not been established. Case reports and small series of subjects indicate that LC control may be observed with the use of highly active targeted therapies like EGFR TKI (Lee et al 2013) or ALK TKI (Riess 2013, Ahn 2012).

There is a medical need for more effective treatment for patients with ALK-positive NSCLC metastatic to the CNS before and after failure to crizotinib.

1.2 Introduction to investigational 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, it is 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 ongoing Phase I clinical trial in patients (with and without previous crizotinib therapy) led to the approval of ceritinib by the Food and Drug Administration (FDA) under the trade name ZYKADIA® on 29-Apr-2014 for the following indication:

[redacted]

- 'ZYKADIA is indicated for the treatment of patients with ALK-positive metastatic 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 indication:

- 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 (Half maximal (50%) inhibitory concentration (IC_{50}) of 0.15 nM for ceritinib and 3 nM for crizotinib). 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 in inhibiting ALK.

Preclinical data showed inhibition of the kinase activity of the NPM-ALK fusion oncogene (in Karpas299 human ALCL cells) and of the EML4-ALK fusion oncogene (in H2228 human NSCLC cells) with ceritinib, which led to inhibition of cancer cell proliferation *in vitro*. Inhibition of the downstream signaling pathway by ceritinib correlated with inhibition of proliferation. In addition, inhibition of 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. A single dose pharmacodynamic study and multiple daily dose efficacy study performed in Karpas299 and H2228 tumor models indicated that a 70% to 80% reduction in the ALK signaling pathway is required to achieve complete tumor regression.

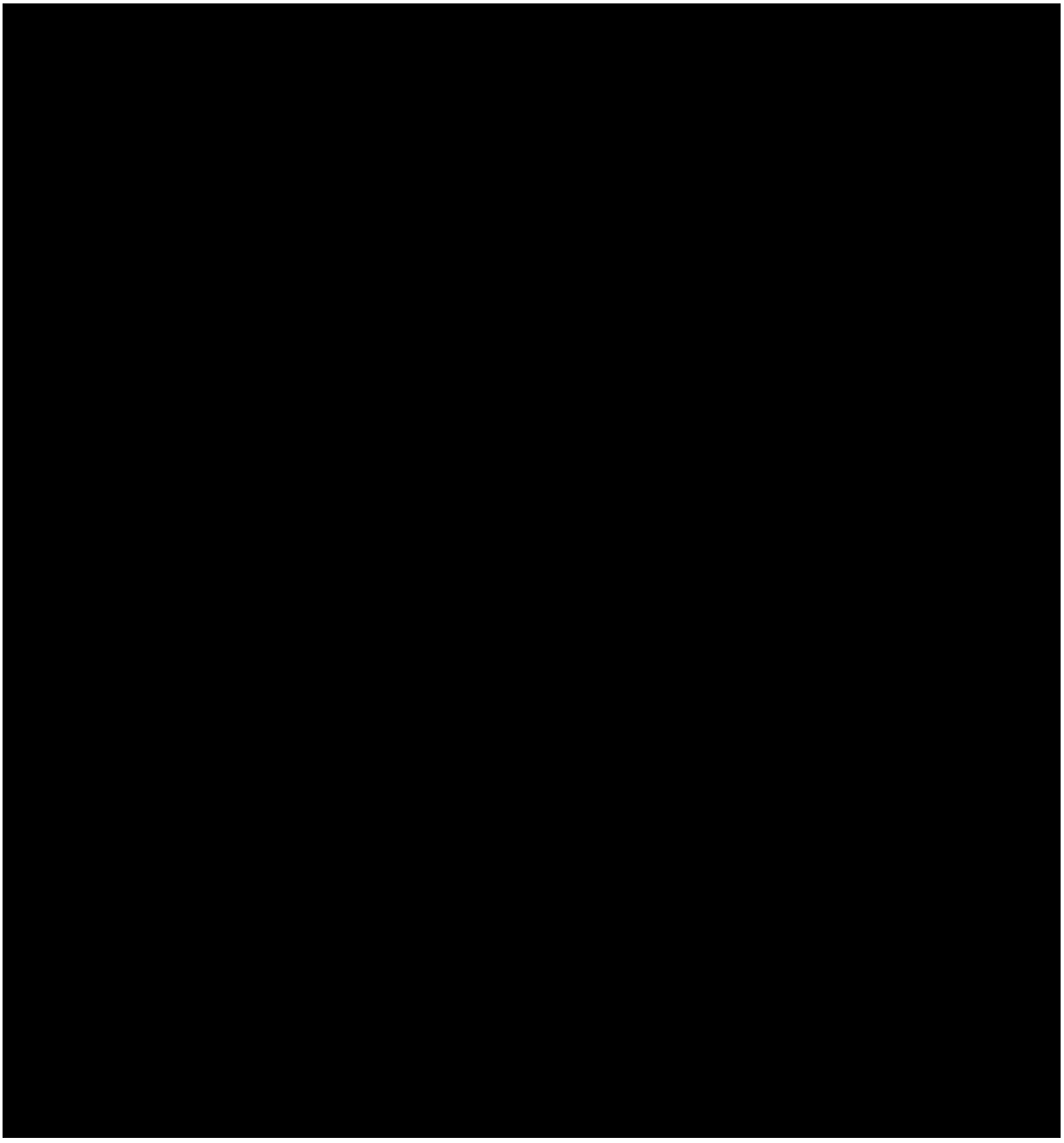
1.2.1.1.2 Antitumor activity in xenograft models

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 25 mg/kg daily, a dose below the maximum tolerated dose (MTD) defined in good clinical practice (GCP) toxicity studies (30 mg/kg in monkey and 50 mg/kg in rat), resulted in complete regression of established tumors. When dosed at 50 mg/kg

[redacted]

daily for 14 days in the H2228 NSCLC model, ceritinib resulted in complete and prolonged tumor regressions (lasting for more than 4.5 months, the observation period). In the same experiments, crizotinib dosed at 100 mg/kg daily for 14 days resulted in complete tumor regression, but tumors re-grew within 2 weeks after stopping treatment.

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.



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1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety and tolerability

Ceritinib is associated with a manageable safety profile. For the 255 patients treated at the recommended dose of 750 mg in the ongoing study [redacted] The

[redacted]

most common adverse events 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%).

Table 1-1 All grades (at least 5%) and grade 3-4 adverse events, regardless of study drug relationship, by preferred term in patients treated in the 750 mg dose group [redacted]

	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
Musculoskeletal Pain	25 (9.8)	0
Anemia	24 (9.4)	9 (3.5)
Edema Peripheral	24 (9.4)	0
Non-Cardiac Chest Pain	24 (9.4)	2 (0.8)
Hypomagnesemia	22 (8.6)	0

[redacted]

	Ceritinib 750 mg N=255	
	All Grades	Grade 3/4
Preferred term	n (%)	n (%)
Productive Cough	22 (8.6)	0
Arthralgia	21 (8.2)	0
Hyperglycemia	21 (8.2)	14 (5.5)
Musculoskeletal Chest Pain	21 (8.2)	0
Lipase Increased	20 (7.8)	13 (5.1)
Pneumonia	20 (7.8)	10 (3.9)
Pain In Extremity	17 (6.7)	0
Muscle Spasms	17 (6.7)	0
Pruritus	17 (6.7)	1 (0.4)
Hyponatremia	16 (6.3)	9 (3.5)
Chest Discomfort	16 (6.3)	0
Dehydration	16 (6.3)	2 (0.8)
Urinary Tract Infection	16 (6.3)	2 (0.8)
Anxiety	16 (6.3)	2 (0.8)
Hypophosphatemia	15 (5.9)	7 (2.7)
Paresthesia	15 (5.9)	0
Influenza	14 (5.5)	0
Tremor	14 (5.5)	0
Gamma-Glutamyl Transferase Increased	13 (5.1)	7 (2.7)
Convulsion	13 (5.1)	6 (2.4)
Upper Respiratory Tract Infection	13 (5.1)	0
Dry skin	13 (5.1)	0
Stomatitis	13 (5.1)	0
Abdominal discomfort	13 (5.1)	0
Rhinorrhea	13 (5.1)	0
Visual Impairment	13 (5.1)	0

Dose reductions due to adverse events (AEs) occurred in 58.4% of patients treated with ceritinib at the 750 mg dose; 38.8% of patients had only 1 dose reduction. AEs 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 discontinuation 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 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) to be monitored for ceritinib have also been identified and include hepatotoxicity, interstitial lung disease/pneumonitis, QT prolongation, bradycardia, hyperglycemia, gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis

[redacted]

(including lipase and amylase elevations). For additional details, refer to the [Investigator's Brochure].

1.2.1.2.2 Clinical efficacy

[redacted], based on investigator assessment, data from the [redacted] Study [redacted] 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). For the corresponding efficacy data based on BIRC review assessment, see Section 1.3. In these patients the 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 CR or PR based on investigator assessment, the median time to response was short at 6.1 weeks (range: 3.0 to 24.1) and 86.1% of the patients achieved a response within 12 weeks. The estimated median DOR based on investigator assessment was long at 9.69 months (95% CI: 7.00, 11.40) (Table 1-3).

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 the patients treated with a prior ALK inhibitor and 6.1 weeks (range: 3.0 to 24.1) in the 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, the median DOR was not reached (95% CI: 9.59, NE) in the ALK inhibitor naïve patients, however the 12-month DOR rate was 65.2% (95% CI: 46.4, 78.8) (Table 1-3). [redacted]

[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) [redacted]

	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 investigator's 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

[redacted]

Table 1-3 Analysis of duration of response based on investigator assessment in NSCLC patients in the 750 mg dose group using Kaplan-Meier method, by prior ALK inhibitor status (Full Analysis Set NSCLC 750 mg– Confirmed PR or CR) [redacted]

	NSCLC with prior ALK inhibitor N=89	NSCLC ALK inhibitor naïve N=55	All NSCLC N=144
No. of events, n (%)	42 (47.2)	14 (25.5)	56 (38.9)
Progression	42 (47.2)	14 (25.5)	56 (38.9)
Death	0	0	0
No. of patients censored	47 (52.8%)	41 (74.5)	88 (61.1)
Kaplan-Meier estimates (%) **DOR rate [95% CI]** at:			
3 months	93.6 [85.4, 97.3]	90.0 [77.6, 95.7]	92.2 [86.0, 95.7]
6 months	56.4 [43.7, 67.4]	73.8 [58.3,84.3]	63.4 [53.7, 71.6]
12 months	17.9 [6.0, 35.1]	65.2 [46.4, 78.8]	33.0 [19.2, 47.6]
25th percentile (month) [95%CI]	4.17 [4.01, 5.09]	5.55 [3.52, NE]	4.21 [4.17, 5.52]
Median (month) [95%CI]	7.39 [5.42, 10.12]	NE [9.59, NE]	9.69 [7.00, 11.40]
75th percentile (month) [95%CI]	11.07 [9.69, NE]	NE [NE, NE]	NE [11.07, NE]

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

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

% Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.

% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of Kaplan-Meier (KM) estimates.

N : Total number of patients included in the analysis.

Based on the investigator assessment 115 PFS events (96 progressions and 19 deaths) were observed, and the median PFS was 8.21 months (95% CI: 6.70, 10.12) with 53.3% of the patients censored. 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) (Table 1-4).

[redacted]

Table 1-4 Analysis of PFS based on investigator assessment in NSCLC patients in the 750 mg dose group, by prior ALK inhibitor status (Full Analysis Set NSCLC 750 mg) [redacted]

	NSCLC with prior ALK inhibitor N=163	NSCLC ALK inhibitor naïve N=83	All NSCLC N=246
Number of PFS events, n (%)	89 (54.6)	26 (31.3)	115 (46.7)
Progression	74 (45.4)	22 (26.5)	96 (39.0)
Death	15 (9.2)	4 (4.8)	19 (7.7)
Number of patients Censored	74 (45.4)	57 (68.7)	131 (53.3)
Kaplan-Meier estimates (%) **PFS rate [95% CI]** at			
3 months	74.6 [66.8, 80.9]	88.1 [78.4, 93.6]	79.2 [73.3, 84.0]
6 months	53.8 [45.0, 61.9]	69.4 [56.7, 79.0]	59.2 [52.0, 65.6]
12 months	28.4 [19.0, 38.6]	61.3 [47.7, 72.3]	39.1 [30.8, 47.4]
25th percentile PFS (month) [95% CI]	2.89 [2.63, 4.27]	5.52 [4.17, 6.90]	4.17 [2.86, 4.63]
Median PFS (month) [95% CI]	6.90 [5.39, 8.41]	NE [8.31, NE]	8.21 [6.70, 10.12]
75th percentile PFS (month) [95% CI]	12.48 [10.12, 12.78]	NE [NE, NE]	NE [12.58, NE]

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

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

% Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.

% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.

N: Total number of patients included in the analysis.

Efficacy analyses were also performed for NSCLC patients in the 750 mg dose group who had brain metastasis (measurable or non-measurable) identified by the investigator at baseline (Table 1-5).

[redacted]

Table 1-5 ORR, DOR and PFS in NSCLC patients with brain metastases at baseline in the 750 mg dose group [redacted]

Efficacy Parameter	NSCLC with prior ALK inhibitor - patients with brain metastases n=98	NSCLC ALK inhibitor naïve - patients with brain metastases n=26	All NSCLC – patients with brain metastases n=124
ORR, n (%) [95% CI]	49 (50.0) [39.7, 60.3]	18 (69.2) [48.2, 85.7]	67 (54.0) [44.9, 63.0]
DOR, median (months) [95% CI]	6.9 [4.8, 8.5]	NE[a] [5.5, NE]	7.0 [5.5, 9.7]
PFS, median (months) [95% CI]	6.7 [4.9, 8.4]	8.3 [4.6, NE]	6.9 [5.4, 8.4]

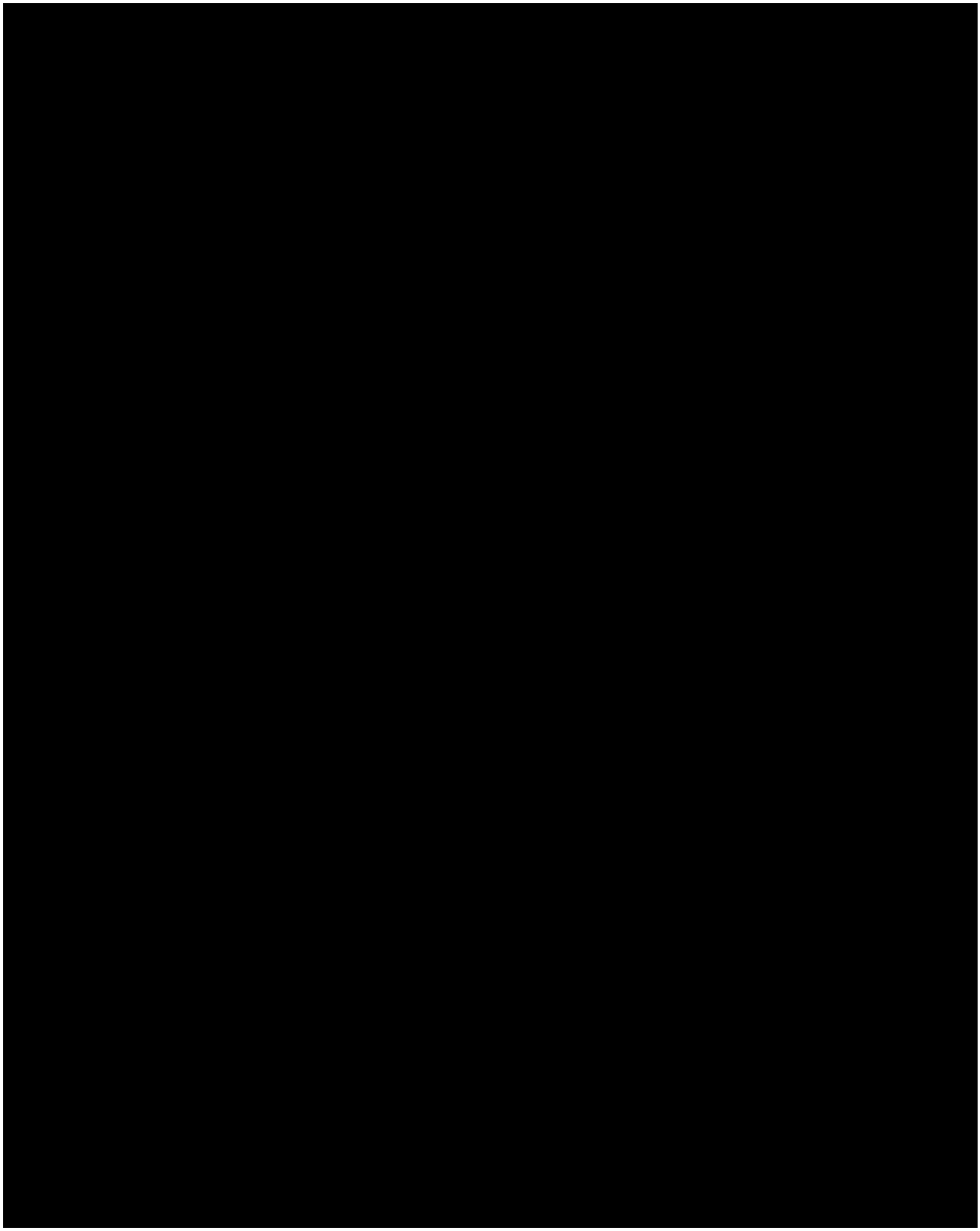
NE: Not estimable
[a] DOR rate at 6 months 65.9% [95% CI: 35.4, 84.5]

A total of 14 patients out of the 246 patients included in the 750 mg dose group had brain metastases at baseline considered to be target lesions by the investigator per RECIST 1.0. In these 14 patients, the OIRR was 50% (95% CI: 23.0, 77.0) (1 patient with confirmed CR in the brain and 6 patients with a confirmed PR in the brain). These responses were observed in 4 patients treated with a prior ALK inhibitor (4 confirmed PR) and in 3 ALK inhibitor naïve patients (1 confirmed CR and 2 confirmed PR).

1.2.1.2.3 Clinical pharmacodynamics

Data are not available from the ongoing clinical studies.

[redacted]



1.3 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, [redacted], 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 [redacted]. 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 [redacted] 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: [redacted], 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 [redacted]. 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 7.1.4.1). 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 6.4. *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 #11).

Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, are extensively described in Section 6.3.4.

[redacted]

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

- Hepatotoxicity: Hepatotoxicity, as defined by TB > 2xULN and ALT and/or AST > 3xULN and ALP < 2xULN, has been observed in <1% of patients treated with ceritinib. 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 #7).
- 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 #19).
- 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 #8).
- 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 ≤ 200 mg/dL (≤ 11.1 mmol/L) at screening (see inclusion #7).
- 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.

a. 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

Brain metastases (BM) are a common complication of patients with NSCLC: 20 to 40% will develop BM within 2 years of diagnosis. BM treatments are usually palliative with the intent to achieve local control of the CNS disease. Treatment options may include surgical resection, stereotactic radiosurgery or whole brain radiation therapy. The combination of these modalities depends on the number and location of the BM. Whole brain radiation therapy is the standard treatment approach for multiple BM leading to a modest overall survival benefit. It is unclear to date if systemic therapies added to local treatment or following local treatment, may achieve a better control of the CNS disease.

In the last decade, research in the NSCLC field has focused on identifying distinct subtypes of NSCLC driven by specific genetic alterations that may be susceptible to targeted inhibition. The remarkable activity of EGFR Tyrosine Kinase inhibitors have changed the way patients harboring activating mutation are treated. EGFR TKI are used as first-line therapy instead of chemotherapy for these patients. Using TKI to inhibit the mutated EGFR affects several cellular regulating functions important in the proliferation and survival of cancer cells, translating into higher response rates and a longer PFS compared to 1st line chemotherapy. Given their low molecular weight, it is assumed that these agents may reach brain metastases more readily and may be more effective than chemotherapies. Small studies reported longer PFS and remarkable clinical activity with EGFR TKI in patients with NSCLC harboring an

activating mutation of EGFR and metastatic to the brain (Fan 2013, Zhuang 2013, Iuchi 2013). These observations open the way to reevaluate the role of systemic treatment for BM when highly effective drugs have a relatively low molecular weight.

ALK, a receptor tyrosine kinase, is involved in the genesis of several cancers through genetic aberrations involving translocation of the kinase domain with multiple fusion partners or activating mutations in the full-length receptor that result in ligand-independent constitutive activation. ALK rearrangement and EGFR mutation are known to be mutually exclusive in NSCLC. Similarly to what is observed with mutated EGFR in NSCLC, ALK rearrangements constitute a key and strong oncogenic driver for NSCLC and represent a critical target susceptible to targeted ALK inhibition. The inhibition of ALK translates into the control of the NSCLC. Crizotinib, the first ALK inhibitor to be evaluated in advanced or metastatic ALK-positive NSCLC patients after failure to a prior platinum-based chemotherapy, achieves a higher response rate (RR) (65%; 95%CI: 58-72) and a longer progression free survival (PFS) compared with second-line chemotherapy (7.7 months versus 3.0 months, HR=0.49; 95% CI, 0.37 – 0.64) (Shaw et al 2013).

Crizotinib may have clinical activity in patients with ALK positive NSCLC metastatic to the brain, but its activity may be less remarkable in the brain than systemically (outside of the brain). Costa et al (2012) measured the concentration of crizotinib in both CSF and plasma and reported that the CSF-to-plasma ratio of crizotinib was 0.0026. Shaw et al (2013) evaluated the progression free survival in a subgroup of patients with or without BM at baseline. The hazard ratio still favored crizotinib compared to second-line chemotherapy in patients with BM (HR=0.67; 95%CI: 0.44 – 1.03) but the results for the subgroup of patients without BM (HR=0.43; 95% CI, 0.30 – 0.60) suggest that crizotinib may not easily cross the blood brain barrier. Crizotinib does not prevent the onset of brain metastases - the brain is the first site of progression in 46% of patients with ALK-positive crizotinib-treated NSCLC (Otterson et al 2012). Another indication that crizotinib has lesser clinical activity in the brain is demonstrated in the low Overall Intracranial Response Rate (OIRR - CR+PR) reported in a group of 109 patients with ALK positive NSCLC with untreated brain metastases at baseline. The OIRR is 7% (95%CI: 3-14) compared to an extracranial Response Rate of 49% (95%CI: 43-63) The OIRR across 22 patients out of the 109, who presented with measurable brain lesion at baseline is 18% (95% CI: 4-40) (Crino et al 2013).

Ceritinib, an orally available ALK inhibitor, is an approximately 20-fold more potent ALK inhibitor than crizotinib. Ceritinib shows potent antitumor activity in patients with ALK-positive advanced or metastatic NSCLC progressing or not on crizotinib.

[redacted], data from the [redacted] Study [redacted] demonstrated a high rate of rapid and durable responses with ceritinib in 246 ALK-positive NSCLC patients treated in the 750 mg dose group. In these patients the ORR was 58.5% (95% CI: 52.1, 64.8) based on investigator assessment. A high ORR of 54.6% and 66.3% was observed in patients treated with a prior ALK inhibitor and the ALK inhibitor naïve patients, respectively, (Table 1-2). 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). Further, the estimated median DOR was 7.39 months (95% CI: 5.42, 10.12) in patients treated with a prior ALK inhibitor, the median DOR was not reached (95%

[redacted]

CI: 9.59, NE) for the ALK inhibitor naïve patients, however the 12-month DOR rate was 65.2% (95% CI: 46.4, 78.8).

A total of 14 patients out of the 246 patients included in the 750 mg dose group had brain metastases at baseline considered to be target lesions by the investigator per RECIST 1.0. In these 14 patients, the OIRR was 50% (95% CI: 23.0, 77.0) (1 patient with confirmed CR in the brain and 6 patients with a confirmed PR in the brain). These responses were observed in 4 patients treated with a prior ALK inhibitor (4 confirmed PR) and in 3 ALK inhibitor naïve patients (1 confirmed CR and 2 confirmed PR).

Leptomeningeal carcinomatosis, another less frequent CNS complication observed in NSCLC, is a rare devastating disease resulting from the seeding of malignant cells to the leptomeninges and cerebrospinal fluid (CSF). LC is observed in approximately 5% of the patients diagnosed with metastatic NSCLC. The incidence of LC in ALK-positive NSCLC may be around 5 to 6% (Gainor et al 2013). Median survival without treatment is about 4-6 weeks and about 3 months with the available treatments (whole brain radiation therapy and intrathecal chemotherapy). The role of systemic treatment for LC is not established. Case reports and small series of subjects indicate that LC control may be observed with the use of highly active targeted therapies like EGFR TKI or ALK TKI (Riess 2014, Lee 2013, Ahn 2012).

There is a medical need for more effective treatment for patients with ALK-positive NSCLC metastatic to the CNS before and after failure to crizotinib. The clinical activity of ceritinib in ALK positive NSCLC patients (progressing or not on crizotinib), its more potent inhibition of ALK and its more favorable brain distribution data in animals compared to crizotinib support the assessment of ceritinib as treatment of patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges, irrespective of prior treatment with an ALK inhibitor.

2.2 Rationale for the study design

This is a phase II, multi-center, open-label, five-arm study to evaluate the efficacy and safety of oral ceritinib treatment for patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges. Only patients whose tumors harbor ALK rearrangement will be enrolled in the study. The study will enroll approximately 160 patients globally.

Patient population

Patients with ALK-positive NSCLC and active metastases into the brain and/or to leptomeninges will be included in this study.

Patients without evidence of leptomeningeal carcinomatosis (LC) will be allocated into one of the following 4 arms taking into account the patient's history of prior therapy: prior radiation therapy (whole brain or stereotactic radiation therapy) to the brain (yes/no) and a prior treatment with an ALK inhibitor (ALKi) (yes/no). Prior ALK inhibitor is limited to treatment with crizotinib in Arms 1, 2, and 5. All patients will have evaluable brain metastases following RECIST 1.1 as per investigator assessment.

The allocation of patients to arm 5 will be independent from the patient's history of prior therapy but rather depend on the presence of neoplastic cells in the cerebrospinal fluid (CSF) as assessed and documented by the investigator at baseline. In the absence of neoplastic cells in the CSF, the allocation of patients to arm 5 will then depend on the diagnosis of typical

[redacted]

radiological leptomeningeal carcinomatosis on the baseline gadolinium-enhanced MRI of the brain (or the spine for suspected LC patients only) by an experienced neuroradiologist.

Table 2-1 Allocation into Study Arms based on prior radiation to brain (yes/no) and prior treatment with ALK inhibitor (yes/no)

	Prior Radiation to the brain: YES	Prior Radiation to the brain: NO
Prior treatment with a ALKi[1]: YES	Arm 1	Arm 2
Prior treatment with a ALKi: NO	Arm 3	Arm 4
Leptomeningeal disease[1]	Arm 5	

[1]Previous treatment with ALK inhibitors other than crizotinib is not allowed in Arms 1, 2 and 5.

The description of patients in each of the five study arms is as follows:

- Arm 1 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously treated with radiation to the brain and with prior exposure to an ALKi.
- Arm 2 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously untreated with radiation to the brain but with prior exposure to an ALKi.
- Arm 3 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously treated with radiation to the brain but with no prior exposure to an ALKi.
- Arm 4 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously untreated with radiation to the brain and with no prior exposure to an ALKi.
- Arm 5 will include any patients with leptomeningeal carcinomatosis with or without evidence of active lesion at the baseline Gadolinium-enhanced brain MRI.

Note: An active brain lesion is a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation). The following lesions are considered active:

- A newly diagnosed brain metastasis in a patient who has never received treatment to the brain or in a patient with previously treated brain metastases.
- A brain lesion previously treated with whole brain radiation will only be considered active when there is an unequivocal size increase in its solid component (cystic component of the lesion is not considered for progression determination) compared to the first available post-radiation radiological evaluation.
- An enlarging brain lesion previously treated with SRS will only be considered active when the nature of the enlargement is clearly attributed to the tumoral component of the lesion and not to the radiation effect.

Whole body, intracranial and extracranial endpoints

Depending on the ability of ceritinib to cross the blood-brain barrier, its therapeutic activity in brain metastases may be different from its activity outside of the brain. This may affect the tumor overall response determined in a population of ALK+ NSCLC patients metastatic into the brain compared to patients without brain metastases. Whole body response and related

[redacted]

endpoints will be evaluated and will include the overall response rate (ORR), duration of response (DOR), disease control rate (DCR) and progression free survival (PFS) for all cancer lesions **in and outside** the brain per RECIST 1.1.

To differentially appreciate this, the intracranial activity of ceritinib **without taking into consideration lesions situated outside of the brain** will be evaluated and reported as an intracranial endpoint.

In contrast, the activity of ceritinib **outside of the brain without inclusion of brain lesions** will be evaluated and will be reported as an extracranial endpoint.

[redacted]

2.3 Rationale for dose and regimen selection

In the dose-escalation phase of [redacted], 59 patients were treated at dose levels of 50 to 750 mg. Eight Dose Limiting Toxicities (DLTs) at Cycle 1 were observed in 6 patients:

- At 400 mg: grade 3 hypophosphatemia in one patient, and grade 3 transaminase increased evolving from grade 2 ALT increased in one patient.
- At 600 mg: grade 3 diarrhea and grade 3 dehydration in one patient each.
- At 750 mg: grade 3 diarrhea with grade 3 vomiting in one patient and intolerable grade 2 diarrhea in one patient.

[redacted] Further confirmation of the 750 mg dose as the appropriate MTD came from the incidence of DLTs in Cycle 1 in the first 10 patients treated at this dose in the expansion phase of the study. There were no first-cycle DLTs in these 10 patients, thus confirming the 750 mg dose as a safe MTD and RD [redacted]

Among the different doses tested, the recommended dose (RD) for the expansion phase was determined to be 750 mg, the highest dose evaluated. The following safety and efficacy considerations were taken into account:

- Safety data indicated that ceritinib is well tolerated at 750 mg for multiple cycles of therapy, without evident difference in the frequency of AEs versus immediate lower doses (400-700 mg).
- Although preliminary efficacy data indicated that tumor responses are observed consistently at doses of 400 mg and above, the response duration appeared to be shorter at

[redacted]

the lower doses. Nonclinical data from ALK-positive NSCLC xenograft models indicated that ceritinib should be dosed at the MTD to maximize efficacy, in particular against crizotinib resistant tumor models.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
The primary objective is to evaluate the antitumor activity of ceritinib in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges based on investigator assessment per RECIST 1.1	The primary endpoint is: ● Overall response rate (ORR), defined as the proportion of patients with a best overall confirmed response of CR or PR in the whole body as assessed per RECIST 1.1 by the investigator.	
Key Secondary Objective		Refer to Section 10.5.
To evaluate Disease Control Rate (DCR) in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges based on investigator assessment per RECIST 1.1	The key secondary endpoint is: ● Disease Control Rate (DCR) in the whole body as assessed per RECIST 1.1 by the Investigator	
Secondary Objectives		Refer to Section 10.5.
1. To evaluate intracranial tumor-response related endpoints as assessed by investigators and Blinded Independent Review Committee (BIRC) (using modified RECIST 1.1 criteria) 2. To evaluate extracranial tumor-response related endpoints as assessed by investigators and BIRC (using RECIST 1.1 criteria) 3. To evaluate whole body tumor-response related endpoints as assessed by investigators and BIRC(using RECIST 1.1 criteria) 4. To evaluate overall survival (OS) in this patient population 5. To evaluate safety in this patient population [redacted]	1. The following intracranial endpoints will be evaluated per modified RECIST 1.1*: ● Overall Intracranial Response Rate (OIRR) by Investigator and BIRC for patients with measurable brain metastases at baseline ● Intracranial Disease Control Rate (IDCR) at 8, 16 weeks and overall by Investigator and BIRC ● Time to intracranial tumor response (TTIR) by Investigator and BIRC for patients with measurable brain metastases at baseline ● Duration of intracranial response (DOIR) by Investigator and BIRC for patients with measurable brain metastases at baseline 2. The following extracranial endpoints will be evaluated per RECIST 1.1: ● Overall Extracranial Response Rate (OERR) by Investigator and BIRC ● Extracranial Disease Control Rate (EDCR) at 8, 16 weeks by Investigator and BIRC ● Time to extracranial tumor response (TTER) by Investigator and BIRC ● Duration of extracranial response (DOER) by Investigator and BIRC 3. The following whole body tumor-response related endpoints will be evaluated per RECIST 1.1: ● Overall response rate (ORR) by BIRC ● Disease control rate (DCR) by BIRC	

[redacted]

Objective	Endpoint	Analysis
	• Time to tumor response (TTR) by Investigator and BIRC • Duration of response (DOR) by Investigator by BIRC • Progression free survival (PFS) by Investigator by BIRC 4. Overall survival (OS) 5. AEs, ECGs, Vital signs and laboratory abnormalities [redacted]	
Exploratory objectives		Refer to Section 10.6.
1. To evaluate intracranial endpoints for patients with measurable brain metastases at baseline in Arms 1 to 4 and for patients with active brain lesions at baseline in Arms 1 to 4 using the Response Assessment in Neuro-Oncology (RANO) criteria for high grade gliomas (Wen et al 2010) by investigators and BIRC. [redacted]	1. Intracranial endpoints including OIRR, Time to Intracranial Tumor Response (TTIR), Duration of Intracranial Response (DOIR) for patients with measurable brain metastases at baseline in Arms 1 to 4, and IDCR in Arms 1 to 4 for patients with active brain lesions at baseline using the Response Assessment in Neuro-Oncology (RANO) criteria for high grade gliomas (Wen et al 2010) by investigators and BIRC. [redacted]	

*RECIST 1.1 will be modified to allow a specific evaluation of the intracranial response to the treatment. The usual criteria to select target lesions will be used but a maximum five target lesions located in the brain can be selected at baseline and evaluated at each assessment time point.

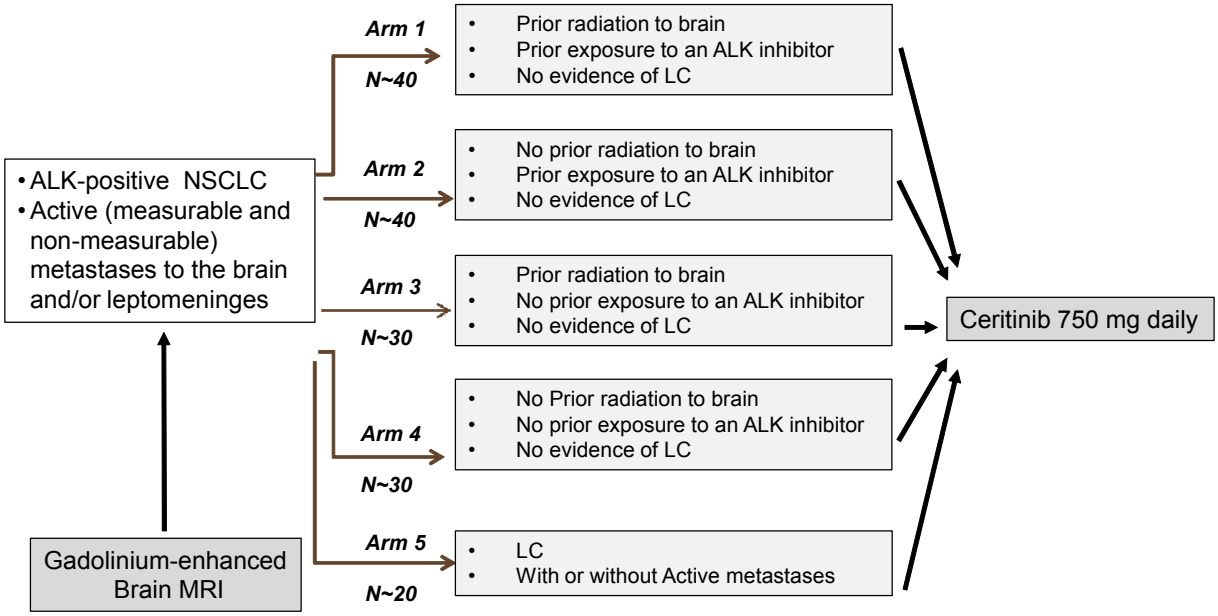
[redacted]

4 Study design

4.1 Description of study design

This is a phase II, multi-center, open-label, five-arm study in which the efficacy and safety of oral ceritinib treatment for patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges will be assessed.

Figure 4-1 Study design



Previous treatment with ALK inhibitors other than crizotinib is not allowed in Arms 1, 2 and 5.

4.1.1 Screening

All patients must harbor an ALK rearrangement as assessed using the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria) **before** initiating treatment with ceritinib.

[redacted]

[redacted]

Eligibility assessment and baseline tumor burden evaluation will be conducted within 28 days prior to starting study drug except for gadolinium-enhanced brain MRI and brain specific eligibility evaluation which should be done within 14 days prior to starting study drug. See Section 7.1.2 for further details.

[redacted]

Following completion of screening procedures and verifying patient eligibility, patients will be allocated to one of the five study arms via IRT.

- Arm 1 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously treated with radiation to the brain and with prior exposure to an ALKi.
- Arm 2 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously untreated with radiation to the brain but with prior exposure to an ALKi.
- Arm 3 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously treated with radiation to the brain but with no prior exposure to an ALKi.
- Arm 4 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously untreated with radiation to the brain and with no prior exposure to an ALKi
- Arm 5 will include any patients with leptomeningeal carcinomatosis with or without evidence of active lesion at the baseline Gadolinium-enhanced brain MRI.

Note: Previous treatment with ALK inhibitors other than crizotinib is not allowed in Arms 1, 2 and 5

Note: An active brain lesion is a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation). The following lesions are considered active:

- A newly diagnosed brain metastasis in a patient who has never received treatment to the brain or in a patient with previously treated brain metastases.
- A brain lesion previously treated with whole brain radiation will only be considered active when there is an unequivocal size increase in its solid component (cystic component of the

[redacted]

lesion is not considered for progression determination) compared to the first available post-radiation radiological evaluation.

- An enlarging brain lesion previously treated with SRS will only be considered active when the nature of the enlargement is clearly attributed to the tumoral component of the lesion and not to the radiation effect.

Approximately 160 patients will be treated in the study, ~40 patients in each Arm 1 and Arm 2, ~30 patients in each Arm 3 and Arm 4, and ~20 patients in Arm 5. Additional patients in Arm 4 may be enrolled in order achieve ~60 patients in Arms 3 and 4 together (i.e. ALKi naïve patients) if enrollment rate in Arm 3 is slow.

Furthermore the study targets to enroll and treat the following number of patients with measurable brain metastasis at baseline as per the investigator's assessment in each of the below subgroups:

- Patients with prior ALKi treatment (combined Arms 1 and 2): ~50 patients with measurable brain metastasis
- Patients with no prior ALKi treatment (combined Arms 3 and 4): ~20 patients with measurable brain metastasis

The measurability of brain metastases will also be assessed by BIRC per RECIST 1.1 on an ongoing basis to target a similar number of patients with measurable brain metastasis at baseline as per BIRC in the above subgroups of patients. Enrollment of patients with only non-measurable brain metastases (even in the presence of extracranial measurable lesions) may be closed in one or more arms if it is determined that the above target for patients with measurable brain metastases will not be met.

4.1.2 Treatment duration

The study treatment phase begins on Cycle 1, Day 1 with the first administration of ceritinib.

All patients will receive the same treatment regimen regardless of the arm to which they are allocated. A cycle of treatment is defined as 28 days of once daily treatment of ceritinib in all study arms.

Treatment with ceritinib will continue until the patient experiences disease progression (in the brain, outside of the brain or both) as determined by the investigator according to RECIST 1.1, unacceptable toxicity that precludes further treatment, pregnancy, start of a new anticancer therapy, discontinues treatment at the discretion of the patient or investigator, lost to follow-up, death, or study is terminated by Sponsor. Exceptions to the discontinuation of study treatment after PD being confirmed by the investigator are described in Section 6.1.3.

4.1.2.1 Tumor assessments during study conduct

Complete tumor assessments including gadolinium enhanced brain MRI will be repeated at Week 8 (on Cycle 3 Day 1) and every 8 weeks (i.e. every 2 cycles) thereafter or earlier if clinically indicated.

Tumor response will be evaluated starting from the first day of treatment with ceritinib until the time of disease progression according to RECIST 1.1 as determined by investigator, withdrawal of consent for further follow-up, loss to follow-up or death. This schedule of

[redacted]

tumor assessment must continue regardless of dose interruptions. In patients who discontinue treatment in the absence of RECIST-defined progression, tumor assessments will continue every 8 weeks until progression of disease, withdrawal of consent for further follow-up, loss to follow-up or death.

For patients presenting with baseline leptomeningeal carcinomatosis with documented malignant cells in the cerebrospinal fluid, CSF samples will be collected at a frequency determined by local clinical practice unless medically contra-indicated. Samples should be obtained from site of disease or initially positive cytology if possible. The investigator may determine if more frequent evaluations are needed in case of suspected disease progression and/or in accordance with local clinical practice. If there are any signs or radiologic or clinical neurological progression, a CSF will be collected if feasible. Clinical progression may be determined based on results of cytological or neurological evaluations.

Gadolinium-enhanced brain MRI scans and all other imaging data collected at baseline and during the conduct of the study will be submitted to the designated imaging vendor for BIRC review.

In this study, standard RECIST 1.1 will be used to evaluate the whole body (including intracranial and extracranial cancer lesions) response endpoints. Assessment of the overall response to treatment and other whole body response related endpoints will be conducted by investigators and BIRC.

Additionally, the intracranial and the extracranial metastatic disease will be evaluated as two separate entities. RECIST 1.1 and RANO for High Grade Glioma (Wen et al 2010) criteria will be used to determine intracranial tumor response based on target brain lesions, if applicable, any non-target brain lesions and any new brain lesions. RECIST 1.1 will be used to evaluate the extracranial tumor response but brain will be excluded from the evaluation.

4.1.2.2 Central radiology review of locally assessed disease progression

In case patients have equivocal disease progression according to RECIST 1.1 (in the brain, outside of the brain or both) as determined by the investigator, a confirmatory tumor assessment should be done at least 4 weeks thereafter. While the investigator is waiting for the confirmatory tumor assessment, it is preferable that the patient continue on study treatment for as long as it is clinically acceptable. However, during this time, the investigator should do whatever is medically necessary for the patient.

If the investigator does not determine disease progression, the patient should continue receiving the study drug unless there is a medical need (i.e., rapid progression or clinical deterioration) for an immediate change in therapy.

If the investigator confirms disease progression, then the patient will discontinue study drug and subsequent follow-up tumor assessments will no longer be required (except in the cases described below).

Exceptions to the discontinuation of study treatment after progressive disease (PD) being confirmed by the investigator are:

- In case of isolated brain progression with controlled disease outside of the brain, patients may continue the study drug during the treatment of the new brain lesion if appropriate. If

[redacted]

ceritinib has to be interrupted during the treatment of the new brain lesions, it may be resumed after the treatment of the brain lesion if:

- Brain lesions are demonstrated to be controlled by gadolinium-enhanced MRI and if patient is neurologically stable within the last 2 weeks prior to the re-initiation of study drug.
- The disease outside of the brain remains controlled prior to re-initiation of study drug. A new tumor assessment will be repeated if the last one available is older than 4 weeks.
- Time interval between last dose and re-initiation of study drug does not exceed 8 weeks.
- Patient will continue to be followed for safety and efficacy assessments as per schedule of assessment.

- If patient had PD outside of the brain (with minimally symptomatic or no PD in the brain) but still derives clinical benefit from ceritinib following investigator's judgment, patient may continue study drug and continue to be followed for safety and efficacy assessments as per schedule of assessment.

In both cases, all imaging data acquired during tumor assessments conducted after PD has been confirmed by the investigator will continue to be submitted to the designated imaging vendor who will send it to the BIRC for review.

If the patient had PD both intracranially and extracranially but still derives clinical benefit from ceritinib following investigator's judgment, patient may continue study drug and continue to be followed for safety assessments as per schedule of assessment.

4.1.2.3 End of Treatment (EOT)

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 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.

Following the cessation of tumor follow-up assessments, patients will be contacted every 3 months to assess patient survival status and/or whether the patient started any other antineoplastic therapies since discontinuing study treatment. Patients do not need to visit the clinic during the survival follow-up.

4.3 End of study

The study will end when both of the following conditions are met:

1. At least 24 weeks after last patient treated in the study.
2. At least 75% of patients have died, have been lost to follow-up, or have withdrawn consent for survival follow-up, **or** the last patient will be able to enter into a separate rollover study and/or other options for continued treatment, whichever comes first.

Patients still treated with the study medication and deriving clinical benefit will be offered to continue the treatment in a separate study (and/or other options for continued treatment with ceritinib that are considered acceptable at the country level such as access to commercially available drug or managed access program). In the separate study, Novartis will continue to supply ceritinib to patients who may benefit from continued treatment as per the Investigator's opinion and safety will be monitored and reported to Health Authorities per regulatory requirements. Prior to the end of the current study (CLDK378A2205), this separate protocol will be submitted to Health Authorities and IRBs involved in the current study.

Primary analysis of any of the study arms or overall will occur only after enrollment in the specific study arms or overall is complete and all patients have completed at least 24 weeks of treatment with ceritinib or have discontinued earlier respectively. A clinical study report (CSR) that includes the primary analysis will be produced. If the end of study criteria is met before the primary analysis is conducted, a single final analysis and study report may be performed. If the end of the study criteria is not met by the time that the primary analysis is conducted, a final CSR will be produced reporting all available data collected up to last patient last visit (LPLV) including the additional study data collected after the primary analysis.

An early primary analysis of specific study arms may be performed before the overall completion of all study arms (i.e. enrollment complete in all five study arms and at least 24 weeks follow up of treated patients unless they have discontinued treatment earlier), if required, due to differential enrollment rate across study arms. If the early analysis is performed for specific study arms a clinical study report (CSR) will be produced including the data from those study arms up to the data cut-off date.

Subsequently, another analysis will be performed after the overall completion of all study arms (i.e. enrollment complete in all five study arms and at least 24 weeks follow up of treated patients unless they have discontinued treatment earlier). This analysis will be considered as primary analysis for the study arms not included in the early analysis and for overall patients. A CSR will be produced that will include data from all study arms up to the data cut-off date.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this occur, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or 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 Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) of the early termination of the trial.

[redacted]

5 Population

5.1 Patient population

Approximately 160 patients diagnosed with ALK-positive metastatic NSCLC (according to the 7th edition of the AJCC Cancer Staging Manual) and active lesions in the brain and/or diagnosed with leptomeningeal carcinomatosis will be included in the study.

Written informed consent must be obtained prior to any screening procedures. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies while on treatment. Laboratory parameters may be retested within the 28-day screening period for an individual patient if such parameters meet an exclusion criterion when initially tested. Rescreening of patients who do not originally meet inclusion and/or exclusion criteria may be allowed at a later stage only after discussion with the sponsor on a case by case basis.

5.2 Inclusion criteria

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

For all patients:

1a. Histologically or cytologically confirmed diagnosis of metastatic NSCLC according to the 7th edition of the AJCC Cancer Staging Manual. In addition, the NSCLC must harbor an ALK rearrangement, as assessed using the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria). If documentation of ALK rearrangement as described above is not locally available, a test to confirm ALK rearrangement must be performed by a Novartis designated central laboratory. Patients must wait for the central laboratory result of the ALK rearrangement status before initiating treatment with ceritinib.

2a. Patients that require ALK rearrangement testing by a Novartis designated central laboratory must have a tumor tissue sample available as an archival sample (if possible obtained after the completion of the patient's last therapeutic regimen) or as a new biopsy. If that is not possible, any tumor biopsy obtained at or since the time of diagnosis can be used (a maximum of two years from biopsy excision is preferred).

3. At least one extracranial measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation. Note: Enrollment of patients with only non-measurable brain metastases may be closed in one or more arms if it is determined that the target for patients with measurable brain metastases across study arms will not be met.
4. Patient is 18 years of age or older at the time of informed consent.
5. Patients may or may not have neurological symptoms but must:
    - Be able to swallow and retain oral medication.

[redacted]

- Be neurologically stable within at least 1 week prior to the first dose of study drug. Neurologically stable is defined as improved or stable neurological examination without increased doses of steroids to manage CNS symptoms within the last 5 days.

6a. Patients may have received prior chemotherapy, crizotinib (other ALK inhibitors are not allowed), biologic therapy or other investigational agents. Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v 4.03). Patients with any grade of alopecia are allowed to enter the study.

- Patients who have been treated with chemotherapy, with biological therapy or other investigational agent must have discontinued the treatment at least 2 weeks (14 days) prior to starting study drug. In case last chemotherapy contains nitrosourea or mitomycin C, the treatment must be discontinued at least 6 weeks prior to the first dose of study drug.
- Patients, if previously treated with crizotinib must discontinue treatment at least 1 week (7 days) prior to the first dose of study drug.

7a. Patient must meet the following laboratory values at the screening visit:

- Absolute Neutrophil Count ≥ 1.5 x 10^9/L
- Platelets ≥ 75 x 10^9/L
- Hemoglobin (Hgb) ≥ 8 g/dL
- Serum creatinine < 1.5 mg/dL and /or calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 30 mL/min
- Total bilirubin ≤ 1.5 x 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 (AST) ≤ 3 x ULN, except for patients with liver metastasis, who are only included if AST ≤ 5 x ULN
- Alanine transaminase (ALT) ≤ 3 x ULN, except for patients with liver metastasis, who are only included if ALT ≤ 5 x ULN
- Alkaline phosphatase (ALP) ≤ 5.0 x ULN
- Serum amylase ≤ 2 x ULN
- Serum lipase ≤ ULN
- Fasting plasma glucose ≤ 200 mg/dL (≤ 11.1 mmol/L)

8. Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements during screening:

- Potassium
- Magnesium
- Phosphorus
- Total calcium (corrected for serum albumin)

9. Patient has life expectancy ≥ 6 weeks.
10. Patient has a WHO performance status 0-2.
11. Patient has the ability to understand and provide signed informed consent.
12. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.

[redacted]

Patients in Arm 1 to 4 must also meet the following inclusion criteria:

13. Patients must have active brain metastases from NSCLC, confirmed by Gadolinium-enhanced MRI without concomitant leptomeningeal carcinomatosis. Dose of steroids must be stable for 5 days before the baseline brain MRI.
    Note: An active brain lesion is a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation). The following lesions are considered active:
    - A newly diagnosed brain metastasis in a patient who has never received treatment to the brain or in a patient with previously treated brain metastases.
    - A brain lesion previously treated with whole brain radiation will only be considered active when there is an unequivocal size increase in its solid component (cystic component of the lesion is not considered for progression determination) compared to the first available post-radiation radiological evaluation.
    - An enlarging brain lesion previously treated with SRS will only be considered active when the nature of the enlargement is clearly attributed to the tumoral component of the lesion and not to the radiation effect.

Patients in Arm 5 must also meet the following inclusion criteria:

14. Patients must be diagnosed with leptomeningeal carcinomatosis. The diagnosis requires either documentation of the presence of malignant cells detected at the cytological examination of the cerebrospinal fluid or a serious suspicion of leptomeningeal carcinomatosis, supported by imaging findings typical of LC on the Gadolinium-enhanced MRI of the brain or spine (in this latter case, the determination of the presence of malignant cells in CSF cytology is strongly recommended).

5.3 Exclusion criteria

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

1. Patient with a history of treatment with ceritinib. Patient with known hypersensitivity to any of the excipients of ceritinib (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate).
2. Patients who need whole brain radiation to control the brain metastases. Patients will not be eligible unless treated brain lesions are progressive or new brain lesions are observed since the post whole brain radiation therapy MRI.
3. In case active brain lesions (single or not) require local treatment but other active brain lesions do not and are not treated, patients will be excluded only if the local treatment (neurosurgical treatment or Stereotactic Radiosurgery) for the brain metastases is conducted within 2 weeks prior to starting study drug. Patients must have recovered from relevant toxicities related to these procedures to grade ≤ 1(CTCAE v 4.03) prior to receiving the first dose of study drug.
4. Planning of any brain local treatment (including but not limited to surgery, stereotactic radiosurgery, whole brain radiation, intrathecal chemotherapy) following the administration of the first dose of study drug.
5. Patient who has received thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and

[redacted]

ribs) radiotherapy ≤ 2 weeks prior to starting the study treatment or has not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to the first dose of study drug is allowed.

6. Patient has had major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to the first dose of study drug or has not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can receive study treatment ≥1 week after the procedure.
7. Patient with a concurrent malignancy or history of a malignant disease other than NSCLC 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.
8. 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 anti-hypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to screening.
   - Ventricular 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).
9. Patient has impairment of GI function or GI disease that may significantly alter the absorption of ceritinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
10. 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 (Appendix 1):
    - Strong inhibitors or strong inducers of CYP3A4/5.
    - Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5 and/or CYP2C9.
    - Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes.
11. Patient is currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants.
12. Patient is receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms (non-CNS), dose

[redacted]

must have been stabilized (or decreasing) for at least 5 days before first dose of study treatment. **Note:** Dose of steroids must be stable for 5 days before the baseline brain MRI.

13. Patient is receiving treatment with any enzyme-inducing anticonvulsant (Appendix 1) 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.
14. Patient is pregnant or nursing (lactating) woman.

15a. 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 study treatment.

16. Sexually active males 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.
17. Patient has other severe, acute, or chronic medical conditions including uncontrolled diabetes mellitus or psychiatric conditions 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.
18. Patient has history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
19. Patient has a history of pancreatitis or a history of increased amylase or lipase that was due to pancreatic disease.
20. Patient has been previously enrolled in the treatment phase of any ceritinib clinical study, regardless of which treatment group the patient was allocated or randomized to.

[redacted]

6 Treatment

6.1 Study treatment

For this study, the term "investigational or study drug" refers to LDK378 (ceritinib). All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record electronic Case Report Form (eCRF).

LDK378 will be provided and supplied by Novartis. LDK378 is supplied as 150 mg hard gelatin capsules as individual open label patient supply. LDK378 will be dosed on a flat scale of 750 mg/day and not be adjusted to body weight or body surface area.

A complete cycle of treatment is defined as 28 days of once daily treatment of LDK378 (ceritinib).

6.1.1 Dosing regimen

LDK378 (ceritinib) will be administered orally once daily at a dose of 750 mg (five 150 mg capsules) on a continuous dosing schedule. The treatment period will start on Cycle 1 Day 1.

Each study site will be supplied with LDK378 by Novartis. LDK378 is supplied as 150 mg hard gelatin capsules as individual patient supply, packaged in bottles. Medication labels for the globally provided study treatment (LDK378) 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. LDK378 will be dispensed by the pharmacist or designee at the investigator's institution.

Patients will self-administer LDK378 on an outpatient basis. The investigator must instruct the patient to take the study drug exactly as prescribed.

The general dose and treatment schedule of the study treatments are listed in Table 6-1.

- All patients should take LDK378 daily at approximately the same time each day in the morning. [redacted]
- Patients should take LDK378 on an empty stomach (i.e. fast from food and drink, except water) at least 1 hour before or 2 hours after a light meal. Each dose of LDK378 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 should 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 usually 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.

[redacted]

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
LDK378	Gelatin capsule for oral use	750 mg (5 x 150 mg / capsule)	Once daily (28 day / cycle)

[redacted]

6.1.2 Guidelines for continuation of treatment

For guidelines for dose modification of treatment, refer to Section 6.3.

6.1.3 Treatment duration

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

- Disease progression (radiologically documented according to RECIST 1.1 in the brain, outside of the brain or both and confirmed by the investigator). Ceritinib therapy will continue until progressive disease has been confirmed by the investigator if clinically acceptable (exceptions to the discontinuation of study treatment after PD being confirmed by the investigator are described below). If the investigator does not determine disease progression, the patient should continue receiving the study drug unless there is a medical need (i.e., rapid progression or clinical deterioration) for an immediate change in therapy
- 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

Exceptions to the discontinuation of study treatment after progressive disease (PD) being confirmed by the investigator are:

- In case of isolated brain progression with controlled disease outside of the brain, patients may resume treatment with study drug after appropriate treatment of the brain lesion if:

[redacted]

- Brain lesions are demonstrated to be controlled by gadolinium-enhanced MRI and if patient is neurologically stable within the last 2 weeks prior to the re-initiation of study drug.
- The disease outside of the brain remains controlled prior to re-initiation of study drug. A new tumor assessment will be repeated if the last one available is older than 4 weeks.
- Time interval between last dose and re-initiation of study drug does not exceed 8 weeks.
- Patient will continue to be followed for safety and efficacy assessments as per schedule of assessment.

- If patient had PD outside of the brain (with minimally symptomatic or no PD in the brain) but still derives clinical benefit from ceritinib following investigator's judgment, patient may continue study drug and continue to be followed for safety and efficacy assessments as per schedule of assessment.

In both cases, all imaging data acquired during tumor assessments conducted after PD has been confirmed by the investigator will continue to be submitted to the designated imaging vendor who will send it to the BIRC for review. In such cases, patients must complete the EOT visit only after permanent discontinuation of ceritinib.

If the patient had PD both intracranially and extracranially but still derives clinical benefit from ceritinib following investigator's judgment, patient may continue study drug and continue to be followed for safety assessments as per schedule of assessment.

6.2 Dose escalation guidelines

Not applicable to this study.

6.3 Dose modifications

6.3.1 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.

General guidelines for dose modifications for toxicities other than those listed in Table 6-3:

For grade 1 and tolerable grade 2 treatment-related toxicities, patients may 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

[redacted]

grade 3 or 4 treatment-related toxicity that is considered by the investigator to be life-threatening, permanently discontinue study treatment.

More detailed ceritinib dose modification guidelines for selected toxicities are described in Section 6.3.3 and Table 6-3. Any planned variance from these guidelines in view of patient safety must first be discussed with the sponsor unless there is an urgent need for action.

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).

6.3.2 Treatment interruption and treatment discontinuation

If the administration of ceritinib is temporarily interrupted for reasons other than toxicity, then treatment with ceritinib may be resumed at the same dose. The same applies if the patient experiences an unacceptable toxicity not specifically described in Table 6-3, provided this toxicity resolved to ≤ CTCAE grade 1.

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

If the treatment with ceritinib dosing 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. See Section 6.1.3 for exception in case of isolated brain progression with controlled disease outside of the brain.

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. Detailed guidelines for follow-up of study drug related AEs or abnormal laboratory values must be followed as described in Section 6.3.4.

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

6.3.3 Criteria for ceritinib dose modifications

A ceritinib dose reduction will follow the guidelines described in Table 6-2. For each patient, a maximum of 3 dose modifications (in 150 mg decrements per reduction) is allowed after which the patient must be discontinued from treatment with ceritinib. Once the dose of ceritinib has been reduced, it cannot be re-escalated. If a patient continues treatment with ceritinib after RECIST-defined PD as determined by the investigator, the criteria for dose modification will also apply.

[redacted]

Table 6-2 Dose reduction steps for ceritinib

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

*Dose reduction should be based on the worst preceding toxicity per NCI-CTCAE version 4.03
**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 6-3.

[redacted]

Table 6-3 Criteria for dose reduction, 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)	Recommendation: Maintain dose level
Grade 4 (ANC < 0.5 x 10^9/L)	Mandatory: Omit dose until resolved to ≤ Grade 2, then it is recommended: If resolved in ≤ 7 days, to maintain dose level If resolved in > 7 days, to ↓ 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)	Mandatory: 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)	Recommendation: Maintain dose level
Grade 3 (PLT < 50 and ≥ 25 x 10^9/L)	Mandatory: Omit dose until resolved to ≤ Grade 2, then it is recommended: If resolved in ≤ 7 days, to maintain dose level If resolved in > 7 days, to ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Mandatory: 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	Recommendation: 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)	Recommendation: Maintain dose level with liver function test (LFTs)*** monitored as per protocol
Grade 2 (> 1.5 and ≤ 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Mandatory: Omit dose until resolved to ≤ Grade 1, then it is recommended: If resolved in ≤ 7 days, to maintain dose level If resolved in > 7 days, to ↓ 1 dose level

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for ceritinib**
Grade 3 (> 3.0 and ≤ 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Mandatory: Omit dose until resolved to ≤ Grade 1, then it is recommended: If resolved in ≤ 7 days, to ↓ 1 dose level If resolved in > 7 days, to discontinue patient from ceritinib
Grade 4 (> 10.0 x ULN)	Mandatory: Permanently discontinue patient from ceritinib
AST or ALT	
Grade 1 (> ULN and ≤ 3.0 x ULN)	Recommendation: 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	Recommendation: 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	Mandatory: Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (> 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Mandatory: Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
AST or ALT and concurrent Total bilirubin	
AST or ALT > 3.0 x ULN with total bilirubin > 2.0 x ULN in the absence of cholestasis or hemolysis	Mandatory: Permanently discontinue patient from ceritinib Refer to Section 6.3.4.2 for additional follow-up
RENAL	
Serum creatinine	
Grade 1 (>1 and ≤1.5 x baseline; >ULN and ≤ 1.5 x ULN)	Recommendation: Maintain dose level
Grade 2 (> 1.5 and ≤ 3 x baseline; >1.5 and ≤3.0 x ULN)	Recommendation: Omit dose until resolved to ≤ Grade 1, then it is recommended: 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)	Mandatory: Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (> 6.0 x ULN)	Mandatory: Permanently discontinue patient from ceritinib
PANCREATIC	
Amylase and/or lipase elevations (in the absence of clinical symptoms)	
Grade 1 (> ULN and ≤1.5 x ULN)	Recommendation: Maintain dose level
Grade 2 (>1.5 - 2.0 x ULN)	Recommendation: Maintain dose level
Grade ≥3 (> 2.0 x ULN)	Mandatory: 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
GASTROINTESTINAL	
Diarrhea**	
Grade 1	Recommendation: Maintain dose level but adjust anti-diarrhea treatment
Grade 2 (despite maximal anti-diarrheal medication)	Recommendation: 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)	Mandatory: Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite maximal anti-diarrheal medication)	Mandatory: Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Nausea***	
Grade 1 or 2	Recommendation: Maintain dose level but adjust anti-emetic treatment
Grade 3 (despite standard anti-emetics)	Mandatory: Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Vomiting***	
Grade 1	Recommendation: Maintain dose level but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Recommendation: 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)	Mandatory: Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite standard anti-emetics)	Mandatory: Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
METABOLIC	
Any Grade **hypophosphatemia**	Recommendation: Treatment with phosphate supplements as clinically indicated and maintain dose level
Persistent **hyperglycemia** (glucose > 250 mg/dL, despite minimization of dose of steroids and optimal anti-hyperglycemic therapy)	Recommendation: 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	Recommendation: Maintain dose level
Grade 3	Recommendation: 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

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for ceritinib**
PULMONARY	
Notes: ● Recommendation: 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, ceritinib dosing may resume at current dose level after the pneumonia resolves.	
PNEUMONITIS	
Any Grade treatment-related ILD/pneumonitis	Mandatory: Permanently discontinue patient from ceritinib
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged******	
Grade 1 (QTc 450-480 ms) Grade 2 (QTc 481-500 ms)	Recommendation: Maintain dose level
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs)	Mandatory: Omit dose until QTc is < 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 [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)	Mandatory: Permanently discontinue patient from ceritinib

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for ceritinib**
Bradycardia	
Grade 1 or 2	Recommendation: Omit dose until recovery to asymptomatic bradycardia (for patients with grade 2 bradycardia) and to a heart rate ≥ 50 bpm or to the baseline heart rate. Evaluate concomitant medications known to cause bradycardia, and adjust the dose of ceritinib. Exception: patients who entered the study with grade 1 bradycardia need only omit dose if bradycardia worsens to grade 2
Grade 3 Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Mandatory: Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 50 bpm or baseline heart rate 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)	Mandatory: Permanently discontinue 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 6.3.4.7) ***** 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 6.3.4.6.) ****** QTcF should be used when evaluating QT prolongation.	

[redacted]

6.3.4 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).

6.3.4.1 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 6-4.

6.3.4.2 Guidelines for the follow-up of laboratory liver abnormalities and potential drug-induced liver injury (DILI) cases

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, ALT, AST, 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 ALT/AST/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 ALT/AST/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 ALT/AST/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. 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 ALT/AST/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 Drug Induced Liver Injury (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:

[redacted]

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- 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 (R <2), hepatocellular (R >5), or mixed (R >2 and <5) 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.

6.3.4.3 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. See Table 6-4.

[redacted]

6.3.4.4 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 4 weeks) (refer to Table 6-4).

If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, withhold ceritinib, assess for history of alcohol consumption and biliary tract disorders, review concomitant medications, and perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.

See also dose modification guidelines described in Table 6-3.

6.3.4.5 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 6-3.

6.3.4.6 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 6-3.

[redacted]

6.3.4.7 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.
- 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 6-3.

6.3.4.8 Guidelines for treatment of hypophosphatemia

In the phase I study [redacted], 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 a 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 with ceritinib. 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.

[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 4 weeks
Investigations (hepatic)	Total bilirubin/ALT/AST 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 frequent) until ≤ Grade 1 Thereafter, continue to test every 2 weeks (or more frequent) 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 frequent) 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: Tests 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 recurrence of ≥ grade 2 event, continue monitoring every cycle (4 weeks)

*Note: this table refers to the evaluation schedule only. Refer to Table 6-3 for dose modifications required for applicable toxicities.

6.3.5 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 6.3.4. Refer to preclinical toxicity and or clinical data found in the [Investigator Brochure].

6.4 Concomitant medications

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient (e.g. such as anti-emetics, anti-diarrhea) is permitted (see Section 6.4.1), except when specifically prohibited (see Section 6.4.2).

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), 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 6.4.2.8), food and or vitamin supplements.

[redacted]

6.4.1 Permitted concomitant therapy

6.4.1.1 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);
- If clinically indicated, corticosteroid therapy such as dexamethasone or prednisone may be used to control CNS tumor associated symptoms. All efforts will be made to minimize the dose of corticosteroids to what is strictly needed and to decrease dose as soon as possible. If dose needs to be increased to control CNS tumor associated symptoms, all efforts will be made to stabilize (or decrease) the dose for at least 5 days before the first dose of study treatment. **Note:** Dose of steroids must be stable for 5 days before the baseline brain MRI. Every effort should be made to maintain a stable (or decreasing) dose of steroids in subsequent brain MRIs.

6.4.1.2 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 evaluated for progressive disease, unless disease progression is excluded and clearly documented in the patients' source documentation. The same guidelines apply to the use of denosumab for the treatment of bone metastatic disease.

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 LDK378 and do not undergo metabolism *in vivo*.

6.4.1.3 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.

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 (Table 14-2 of Appendix 1). 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

[redacted]

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 6.4.2.5).

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

6.4.1.4 Non-enzyme inducing anti-epileptic drugs

Non-enzyme inducing anti-epileptic medication (Non-EIAED) is allowed. See Table 14-3 of Appendix 1.

6.4.1.5 Palliative radiotherapy and surgery

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture, or for progression of the brain metastases may be carried out if required. 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.

For patients with a RECIST-documented PD into the brain that are candidates to continue study drug beyond progression (see Section 6.1.3 for exceptions to study drug discontinuation), as determined by the Investigator, may undergo radiotherapy and/or surgical resection as palliative localized therapy to treat metastatic lesions.

In any situation, when radiotherapy or surgery is required, ceritinib should be held for at least 4 days prior to radiotherapy and at least 1 day prior to any surgery and may be resumed ≥3 days after completing radiotherapy or minor surgery, and ≥2 weeks after major surgery.

6.4.1.6 Gastric protection agents

The use of gastric protection agents including antacids, H2-antagonists, and proton pump inhibitors (PPIs; Table 14-2 of Appendix 1) is allowed. 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).

6.4.2 Prohibited concomitant therapy

6.4.2.1 Other anticancer therapy

Anticancer therapy (chemotherapy, targeted therapy, biologic therapy or radiation therapy (except palliative radiotherapy and palliative surgery as described in Section 6.4.1.5), 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

[redacted]

must be permanently discontinued from the treatment portion of the study. See Section 6.1.3 for exceptions in case of isolated brain progression with controlled disease outside of the brain.

6.4.2.2 Other investigational therapies

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

6.4.2.3 Warfarin and coumarin derivatives

Therapeutic doses of warfarin sodium or any other coumarin-derivative anticoagulant are not permitted. Ceritinib is an inhibitor of 2C9, the major metabolizing enzyme of warfarin. A clinically relevant increase in warfarin exposure is possible.

6.4.2.4 Enzyme inducing anti-epileptic drug

Use of EIAEDs is not permitted. Refer to Table 14-3 of Appendix 1 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.

6.4.2.5 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 Table 14-1 of Appendix 1 for a list of these medications. Please note that this list may not be comprehensive.

6.4.2.6 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 Table 14-1 of Appendix 1 for a list of these medications. Please note that this list may not be comprehensive.

6.4.2.7 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.

[redacted]

6.4.2.8 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 [redacted]. 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 administration of ceritinib with drugs known to have a high risk of increasing the QTc interval, and drugs known to increase the QTc interval that are also primarily metabolized by CYP3A4/5 should be avoided. Concomitant use of ceritinib and any medication included in Table 14-4 of Appendix 1 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.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject 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 Subject No. available to the investigator through the Oracle Clinical Remote Data Capture interface.

At the pre-screening and screening visit, the investigator or designated staff will contact the Interactive Response Technology (IRT) system and provide the requested identifying information for the patient to register them into the IRT system. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition eCRF page.

If the patient is a screen failure, IRT should be notified within 2 working days that the patient was a screen failure and was not enrolled.

[redacted]

6.5.2 Treatment assignment

Following completion of pre-screening and screening procedures the IRT system must again be contacted to verify patient eligibility, allocation to one of the five study arms and enroll the patient in the study before the patient receives the first dose on C1D1.

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

All patients will receive the same treatment regimen regardless of the arm to which they are allocated. A cycle of treatment is defined as 28 days of once daily treatment of ceritinib in all study arms.

6.5.3 Treatment blinding

Not applicable.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as per protocol. Study drug will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

The site pharmacy will receive open label medication containing LDK378 capsules. Medication will be dispensed based on the appropriate dose with instructions from the investigator on how to take the medication.

Table 6-5 Preparation and dispensing

Study treatments	Dispensing	Preparation
LDK378	Capsules including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	Not applicable

[redacted]

[redacted]

[redacted]

6.6.2 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].

6.6.3 Study drug compliance and accountability

6.6.3.1 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.

Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee.

6.6.3.2 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.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility or third party, as appropriate, or locally at the site only if permitted by local regulations and authorized by Novartis.

[redacted]

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. Each treatment cycle is 28 days (the 28 days cycle length is fixed regardless of whether the dose of ceritinib is withheld). All visits are to be scheduled according to the appropriate number of calendar days from Cycle 1 Day 1 of study drug administration. A visit window of +/- 1 day in Cycle 1 and +/- 3 days in Cycle 2 onwards is allowed. Imaging evaluations may be performed +/-7 days of the due date of the assessment. **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.**

All data obtained from these assessments must be supported in the patients' 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 only (S).

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol section		Screening Phase (Day -28 to Day -1)		Treatment Phase					Post treatment follow up phase		Survival follow-up phase
						Cycle 1 (28 days)			Subsequent cycles (28 days)	End of treatment (EOT)			
Visit name			**Molecular Pre-Screening**	**General Screening**	**Brain specific evaluation (Day -14 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up if no PD - at the EOT**	**End of post-treatment evaluation (Study Phase completion)**	**Survival follow-up**
Obtain molecular pre-screening ICF and IRT registration	D	7.1.2.	X										
Collect tumor biopsy, either archival or new tumor sample for ALK rearrangement testing	D	7.1.1.	X										
ALK test performed on archival specimen or in newly obtained tumor tissue biopsy at NVS central laboratory	D	7.1.1.1.	X										
Confirmation of ALK status by central laboratory	D	7.1.1. 7.1.2.	X										
Obtain Main Informed Consent and IRT registration	D	7.1.2.	X* (see footnote)	X									
[redacted]													

[redacted]

	Category	Protocol section		Screening Phase (Day -28 to Day -1)		Treatment Phase					Post treatment follow up phase		Survival follow-up phase
						Cycle 1 (28 days)			Subsequent cycles (28 days)	End of treatment (EOT)			
Visit name			**Molecular Pre-Screening**	**General Screening**	**Brain specific evaluation (Day -14 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up if no PD - at the EOT**	**End of post-treatment evaluation (Study Phase completion)**	**Survival follow-up**
[redacted]													
End of Phase Disposition Page	D	7.1.		X Screening Phase Disposition (eCRF)						X End of Treatment Phase Completion (eCRF)		X End of Post-Treatment Follow-Up	
Demography	D	7.1.2.2.	X										
Inclusion/ exclusion criteria	D	5.1. 5.2.		X									
Eligibility check	D	6.5.1.		X									
Allocation to study arms via IRT	D	6.5.2.		X									
Relevant medical history/ current medical conditions	D	7.1.2.3.		X									
Smoking history	D	7.1.2.3.		X									
Diagnosis and extent of cancer	D	7.1.2.3.		X									
Prior antineoplastic therapies (meds, surgery, radiation)	D	7.1.2.3.		X									

[redacted]

	Category	Protocol section		Screening Phase (Day -28 to Day -1)		Treatment Phase					Post treatment follow up phase		Survival follow-up phase
						Cycle 1 (28 days)			Subsequent cycles (28 days)	End of treatment (EOT)			
Visit name			**Molecular Pre-Screening**	**General Screening**	**Brain specific evaluation (Day -14 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up if no PD - at the EOT**	**End of post-treatment evaluation (Study Phase completion)**	**Survival follow-up**
Prior and concomitant medication	D	7.1.2.3.		Continuous							X	X	
Neurological examination	S	7.2.2.5.			X	X		X	X	X	X	X	
Physical examination	S	7.2.2.1.		X		X		X	X	X			
Performance status (WHO)	D	7.2.2.4.		X		X			X	X			
Height	D	7.2.2.3.		X									
Weight	D	7.2.2.3.		X		X			X	X			
Vital signs	D	7.2.2.2.		X		X	X	X	X	X			
Hematology	D	7.2.2.6.1.		X		X		X	X	X			
Blood chemistry	D	7.2.2.6.2.		X		X		X	X	X			
Urinalysis (dipstick) with micro-analysis	D	7.2.2.6.3.		X									
Serum pregnancy test	D	7.2.2.6.4.		X									
Urine pregnancy test (prior to dosing)	D	7.2.2.6.4.				X			X	X			
Coagulation	D	7.2.2.6.5.		X									

[redacted]

	Category	Protocol section		Screening Phase (Day -28 to Day -1)		Treatment Phase					Post treatment follow up phase		Survival follow-up phase
						Cycle 1 (28 days)			Subsequent cycles (28 days)	End of treatment (EOT)			
Visit name			**Molecular Pre-Screening**	**General Screening**	**Brain specific evaluation (Day -14 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up if no PD - at the EOT**	**End of post-treatment evaluation (Study Phase completion)**	**Survival follow-up**
CT scan or MRI of chest and abdomen	D	7.2.1.		X					X Starting on C3D1 then every 2nd cycle (i.e. every 8 weeks)	X	X Every 8 weeks following EOT until PD		
Whole body bone scan	D	7.2.1.		X									
Gadolinium-enhanced brain MRI	D	7.2.1.			X				X Starting on C3D1 then every 2nd cycle (i.e. every 8 weeks)	X	X Every 8 weeks) following EOT until PD		

[redacted]

	Category	Protocol section		Screening Phase (Day -28 to Day -1)		Treatment Phase					Post treatment follow up phase		Survival follow-up phase
						Cycle 1 (28 days)			Subsequent cycles (28 days)	End of treatment (EOT)			
Visit name			**Molecular Pre-Screening**	**General Screening**	**Brain specific evaluation (Day -14 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up if no PD - at the EOT**	**End of post-treatment evaluation (Study Phase completion)**	**Survival follow-up**
CT scan or MRI of other metastatic sites (e.g. neck, spine, pelvis, 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 CT scan or MRI). Photography (for any skin lesions)	D	7.2.1.		X (if clinically indicated)					X Starting on C3D1 then every 2nd cycle (i.e. every 8 weeks) only if positive at baseline or clinically indicated	X Only if positive at baseline or clinically indicated	X Every 8 weeks) following EOT until PD; only if positive at baseline or clinically indicated		
Ceritinib administration	D	6.1.1.				Continuous daily dosing							
Adverse events	D	8.1.		Continuous									
ECG	D	7.2.2.7.1.		X		X	X	X	X	X			
[redacted]													
Meal record	D	7.2.3.1.							C2D1				

[redacted]

	Category	Protocol section		Screening Phase (Day -28 to Day -1)		Treatment Phase					Post treatment follow up phase		Survival follow-up phase
						Cycle 1 (28 days)			Subsequent cycles (28 days)	End of treatment (EOT)			
Visit name			**Molecular Pre-Screening**	**General Screening**	**Brain specific evaluation (Day -14 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up if no PD - at the EOT**	**End of post-treatment evaluation (Study Phase completion)**	**Survival follow-up**
[redacted]													
Healthcare Resource Utilization	D	7.2.6.				X - Continuous							
Antineoplastic therapies since discontinuation of study treatment	D	7.1.6.3.									X		X Every 12 weeks
Survival assessment	D	7.1.6.3.											X Every 12 weeks

[redacted]

	Category	Protocol section		Screening Phase (Day -28 to Day -1)		Treatment Phase					Post treatment follow up phase		Survival follow-up phase
						Cycle 1 (28 days)			Subsequent cycles (28 days)	End of treatment (EOT)			
Visit name			**Molecular Pre-Screening**	**General Screening**	**Brain specific evaluation (Day -14 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up if no PD - at the EOT**	**End of post-treatment evaluation (Study Phase completion)**	**Survival follow-up**
* Patients that have locally available source documentation with confirmed ALK positive rearrangement by the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria) may directly proceed with signing the Main informed consent form (ICF) and conducting evaluations associated with the screening visit to determine eligibility before initiating treatment with ceritinib. These patients will still have to be first registered in IRT as having undergone Molecular pre-screening phase before proceeding to screening phase in IRT. Patients without locally available source documentation (as described above) must sign pre-screening ICF and wait for the central laboratory results of the ALK rearrangement status before entering the screening phase of the CLDK378A2205 study.													

[redacted]

[redacted]

7.1.1.1 Tumor sample requirements for central laboratory analysis

[redacted]

Re-pre-screening of patients with an ALK-negative status confirmed by a Novartis-designated central laboratory may be allowed only after discussion with the sponsor on a case by case basis. The ALK status (positive or negative) will be registered in IRT upon final confirmation from the Novartis-designated central laboratory.

[redacted]

[redacted]

[redacted]

[redacted]

7.1.2 Screening

[redacted]

Rescreening of patients during the screening period may be allowed and laboratory parameters may be retested within the 28-day screening window (day -28 to day -1) period for an individual patient if such parameters meet an exclusion criterion when initially tested.

Laboratory assessments performed as part of the screening evaluations will not be required to be repeated prior to dosing (except urine pregnancy test) unless deemed clinically necessary by investigator and/or required as per local institutional policies. The cardiac eligibility criteria should be assessed with the central ECG report. Tumor imaging assessments will be performed at screening between Day -28 and Day -1 except for brain specific eligibility evaluations which will be performed between Day -14 and Day -1.

[redacted]

Imaging assessments other than imaging of the brain or spine imaging 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.

Brain or spine MRI already completed during the regular work-up of the patient within 14 days prior to start of treatment, including before signing the main study ICF can be considered as the baseline images for this study.

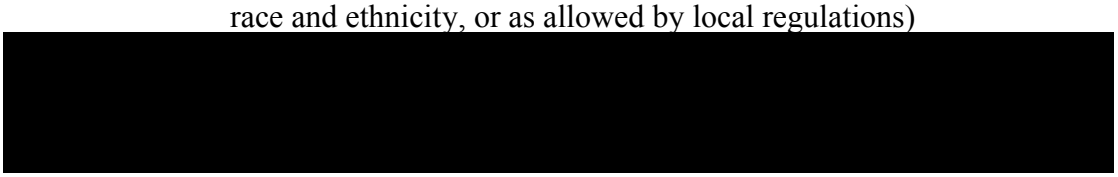
7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Allocation to one of the five study arms will also be registered via IRT. Please refer to and comply with the detailed guidelines in the IRT manual.

7.1.2.3 Patient demographics and other baseline characteristics

Data to be collected on patient characteristics at pre-screening and screening include:

- Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)



- Relevant medical history
- History of smoking
- NSCLC diagnosis and extent of disease, including:
  - Date of diagnosis of NSCLC
  - ALK status documentation
  - Site of active disease
  - Characteristics of disease
  - Concomitant molecular alteration when available (and results of all the tests performed even if wild type)
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and Concomitant Medications, surgical and medical procedures
- Neurological examination and use of steroids to control CNS symptoms

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.

7.1.3 Treatment period

The study treatment phase begins on Cycle 1, Day 1 with the first administration of ceritinib. Treatment with ceritinib will continue until the patient experiences disease progression (in the brain, outside of the brain or both) as determined by the investigator according to RECIST 1.1, unacceptable toxicity that precludes further treatment, pregnancy, start of a new anticancer therapy, discontinues treatment at the discretion of the patient or investigator, lost to follow-up, death, or study is terminated by Sponsor. Exceptions to the discontinuation of study drug upon confirmation of PD by the investigator are detailed in Section 4.1.2.2.

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

Visit windows of ± 1 calendar day will be applicable to scheduled study assessments during Cycle 1. Visit windows of ± 3 days from scheduled study assessments will apply during and beyond Cycle 2. The only exception is imaging assessments, which have a ± 7 day window at all scheduled time points.

7.1.4 End of treatment visit including study completion or discontinuation

A patient will be defined as on the study if they are continuing to have any study data collected, i.e. if the patient is being treated with ceritinib, is in efficacy follow-up after discontinuing ceritinib or is in survival follow-up.

7.1.4.1 Study treatment discontinuation

Patients may voluntarily withdraw from study treatment at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g., telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. They may be considered withdrawn if

[redacted]

they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

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 (radiological as assessed by investigator)
- 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 study treatment during the treatment phase should be scheduled for a visit as soon as possible and within 7 days 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, giving the date and reason for stopping ceritinib treatment.

Exceptions to the discontinuation of study treatment after progressive disease (PD) being confirmed by the investigator are:

- In case of isolated brain progression with controlled disease outside of the brain, patients may resume treatment with study drug after appropriate treatment of the brain lesion if:
  - Brain lesions are demonstrated to be controlled by gadolinium-enhanced MRI and if patient is neurologically stable within the last 2 weeks prior to the re-initiation of study drug
  - The disease outside of the brain remains controlled prior to re-initiation of study drug. A new tumor assessment will be repeated if the last one available is older than 4 weeks.
  - Time interval between last dose and re-initiation of study drug does not exceed 8 weeks
  - Patient will continue to be followed for safety and efficacy assessments as per schedule of assessment.

[redacted]

- If patient had PD outside of the brain (with minimally symptomatic or no PD in the brain) but still derives clinical benefit from ceritinib following investigator's judgment, patient may continue study drug and continue to be followed for safety and efficacy assessments as per schedule of assessment.

In both cases, all imaging data acquired during tumor assessments conducted after PD has been confirmed by the investigator will continue to be submitted to the designated imaging vendor who will send it to the BIRC for review. In such cases, patients must complete the EOT visit only after permanent discontinuation of ceritinib.

If the patient had PD both intracranially and extracranially but still derives clinical benefit from ceritinib following investigator's judgment, patient may continue study drug and continue to be followed for safety assessments as per schedule of assessment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the survival status.

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.

If a patient discontinues study treatment, but continues study assessments, (e.g. during post treatment follow up phase as detailed in Table 7-1), the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the End of Post Treatment (Study Phase Completion) Disposition eCRF page.

The Investigator must contact the IRT to register the patient's discontinuation from treatment.

Patients who discontinue study treatment should enter the survival follow-up period or continue tumor assessments when appropriate. Tumor assessments will continue until investigator's determined disease progression, patient withdraws consent from tumor assessments, patient is lost to follow-up, death or study terminated by Sponsor.

7.1.4.2 Replacement policy

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

7.1.5 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data.

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

[redacted]

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessments table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and ROW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.6 Follow up for safety evaluations

7.1.6.1 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.

7.1.6.2 Post-treatment follow-up

All patients who discontinued treatment during the treatment phase for reasons other than death, lost to follow-up, pregnancy or disease progression as per investigator assessment (Section 7.1.3) will continue tumor assessments as per Table 7-1 (every 8 weeks) thereafter until PD as per investigator assessment, withdrawal of consent or death. Once the patient ceases tumor follow-up, the reason for completion should be recorded on the End of Post Treatment Disposition (Study Phase Completion) eCRF page.

7.1.6.3 Survival follow-up

All patients who had PD as per investigator assessment, have started a new anti-neoplastic therapy, and/or withdrew consent from further study assessments will subsequently be followed for survival information every 12 weeks until death, lost to follow-up or withdrawal of consent for survival follow-up. The investigator or his designee will collect this survival

[redacted]

information and any new anti-neoplastic therapies for all patients until the final survival analysis.

Follow-up can be done via a phone contact. Antineoplastic therapies will be captured on the 'Antineoplastic therapies since discontinuation of study treatment' eCRF page following the last dose of the study treatment.

7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Whole body and extracranial tumor response will be assessed by investigator and by BIRC according to the Novartis guideline version 3.1 (Appendix 2) based on RECIST 1.1 (Eisenhauer et al 2009).

Additionally, intracranial tumor response will be assessed by investigator and by BIRC using modified RECIST 1.1 and the Response Assessment in Neuro-Oncology (RANO) criteria for high grade gliomas (Wen et al 2010) (Appendix 3).

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. Patient neurological status, corticosteroid dose and cytology results, as well as, information regarding prior interventions and pre-existing radiographic findings that mimic metastatic disease at baseline/screening, should also be transmitted to the imaging CRO for review by BIRC. Further details regarding transmission of the information can be found in the imaging CRO site operations manual.

The imaging assessment collection plan is presented in Table 7-2.

Table 7-2 Imaging assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI of Chest and Abdomen	Mandated	Mandated at week 8 on Cycle 3 Day 1, then every 2nd cycle (i.e., every 8 weeks)
Gadolinium enhanced MRI of the brain	Mandated	Mandated at week 8 on Cycle 3 Day 1, then every 2nd cycle (i.e., every 8 weeks)
Whole body bone scan	Mandated	If clinically indicated
• Spine MRI (for suspected LC patients only) • CT scan or MRI of other metastatic sites (e.g., neck, pelvis, 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) • Photography (for any skin lesions)	Only if clinically indicated	At week 8 on Cycle 3 Day 1, then every 2nd cycle (i.e., every 8 weeks) only if positive at baseline or clinically indicated

7.2.1.1 Baseline imaging (+/- photography) assessment

Imaging assessments will be performed at screening/baseline Day -28 to Day -1 prior to Cycle 1 Day 1 except for brain specific eligibility evaluations which will be performed between Day -14 and Day -1.

Any imaging assessments other than imaging of the brain or spine imaging 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. Any brain or spine imaging assessments already completed during the regular work-up of the patient within 14 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study.

Any imaging assessments obtained after first dose of study drug cannot be considered baseline images. The following assessments are required at screening/baseline:

- CT scan or MRI of chest and abdomen
- Gadolinium enhanced MRI of the brain (and spine for suspected LC patients only)
- Whole body bone scan
- Additional CT scan or MRI of other metastatic sites (e.g., neck, pelvis, 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)
- Photography (for any skin lesions) if clinically significant

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.

[redacted]

Gadolinium-enhanced MRI of the brain (and spine for suspected LC patients only) will be used at each efficacy assessment time point. If technically possible, slice thickness should preferably be 1 mm, but it should not exceed 5 mm.

A whole body bone scan should be performed per institutional standard of care for all patients to detect any skeletal metastases present [e.g., Tc-99 bone scan, whole body bone MRI, FDG-PET or sodium fluoride positron emission tomography (NaF PET)]. Localized CT, MRI or X-rays 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, pelvis) of disease as appropriate should be performed.

Color photography, including a metric ruler to estimate the size of the lesion, must be acquired for all skin lesions present per instructions provided in the photography manual from the designated vendor.

Chest x-ray and ultrasound should not be used for lesion evaluation in this study.

Required conditions for baseline tumor assessment

Patients will be allocated into one of the following 5 arms based on investigator assessment at baseline:

- Arm 1 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously treated with radiation to the brain and with prior exposure to an ALKi.
- Arm 2 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously untreated with radiation to the brain but with prior exposure to an ALKi.
- Arm 3 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously treated with radiation to the brain but with no prior exposure to an ALKi.
- Arm 4 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously untreated with radiation to the brain and with no prior exposure to an ALKi
- Arm 5 will include any patients with leptomeningeal carcinomatosis with or without evidence of active lesion at the baseline Gadolinium-enhanced brain MRI.

Note: Previous treatment with ALK inhibitors other than crizotinib is not allowed in Arms 1, 2 and 5

An active brain lesion is a lesion free of any local treatment (like stereotactic radiosurgery or whole brain radiation). The following lesions are considered active:

- A newly diagnosed brain metastasis in a patient who has never received treatment to the brain or in a patient with previously treated brain metastases.
- A brain lesion previously treated with whole brain radiation will only be considered active when there is an unequivocal size increase in its solid component (cystic component of the

[redacted]

lesion is not considered for progression determination) compared to the first available post-radiation radiological evaluation.

- An enlarging brain lesion previously treated with SRS will only be considered active when the nature of the enlargement is clearly attributed to the tumoral component of the lesion and not to the radiation effect.

Whole body: All tumor assessments conducted at each time point will be used to evaluate the response to treatment. Standard RECIST 1.1 will be used at baseline to select target and non-target lesions located in the brain and outside of the brain and to assess the overall response to the treatment.

In the brain: Gadolinium-enhanced MRI of the brain (if technically possible, slice thickness should preferably be 1 mm, but it should not exceed 5 mm) will be used at each efficacy assessment time point (starting at Week 8 and every 8 weeks thereafter) to evaluate the brain lesions. RECIST 1.1 will be modified to allow a specific evaluation of the intracranial response to the treatment. The usual criteria to select target lesions will be used but a maximum five target lesions located in the brain can be selected at baseline and evaluated at each assessment time point. Brain non-target lesions will be recorded at baseline and evaluated at each time point. OIRR will be assessed on the brain target lesions, brain non-target lesions and brain new lesions and will follow the standard RECIST 1.1 criteria for response. The RANO criteria will be utilized in conjunction with the RECIST 1.1 criteria specifically to evaluate intracranial endpoints in each of arm 1, arm 2, arm 3 and arm 4 for patients with active brain lesion at baseline.

Outside of the brain: CT scan or MRI of the chest and abdomen and a whole body bone scan will be conducted at baseline. Additionally, localized CT, MRI or X-rays of all skeletal lesions identified at screening will be performed if not visible on the chest, abdomen and pelvis CT (or MRI). CT scan or MRI of the chest and abdomen will be conducted at each tumor assessment time point (starting at Week 8 and every 8 weeks thereafter) along with other positive tests at baseline per Table 7-1. Other assessments may be indicated in case of clinically suspected progression. RECIST 1.1 will be used to allow a specific evaluation of the extracranial response to treatment. Only lesions located outside of the brain will be considered for the selection of target and non-target lesions at baseline, and evaluated at each assessment time point. OERR will be assessed on the target lesions, non-target lesions and new lesions located outside of the brain and will follow the standard RECIST 1.1 criteria for response.

Leptomeningeal carcinomatosis: Gadolinium enhanced MRI of the brain **and** spine (if technically possible, slice thickness should preferably be 1 mm, but it should not exceed 5 mm) will be used at each assessment time point starting at Week 8 and every 8 weeks thereafter. For patient presenting with a baseline leptomeningeal carcinomatosis with documented malignant cells in the cerebrospinal fluid, CSF will be collected at a frequency determined by local clinical practice unless medically contraindicated.

7.2.1.2 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).

[redacted]

Tumor assessment for response determination will be made every 8 weeks starting from Day 1 of cycle 3 (+/- 7 days window). **The 8 weeks interval should be respected regardless of whether treatment with ceritinib is temporarily withheld.**

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. At the discretion of the Investigators, FDG-PET scans may be performed to document PD per RECIST 1.1 (Appendix 2).

All study imaging (including any off-schedule imaging studies) performed to evaluate progression or response should be submitted to the designated imaging vendor for quality control and review by the BIRC. If an off-schedule scan is performed for response confirmation purposes, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

7.2.1.3 Transmission of efficacy data to BIRC

All radiological assessments will be read locally and should be submitted promptly after acquisition to the imaging CRO designated by Novartis. [redacted]

In case patients have equivocal disease progression according to RECIST 1.1 (in the brain, outside of the brain or both) as determined by the investigator, a confirmatory tumor assessment should be done at least 4 weeks thereafter. While the investigator is waiting for the confirmatory tumor assessment, it is preferable that the patient continues on study treatment for as long as it is clinically acceptable. However, during this time, the investigator should do whatever is medically necessary for the patient.

[redacted]

If the investigator does not determine disease progression, the patient should continue receiving the study drug unless there is a medical need (i.e., rapid progression or clinical deterioration) for an immediate change in therapy.

If the investigator confirms disease progression, then the patient will discontinue study drug and subsequent follow-up tumor assessments are no longer required (except in the cases described below).

Exceptions to the discontinuation of study treatment after progressive disease (PD) being confirmed by the investigator are:

- In case of isolated brain progression with controlled disease outside of the brain, patients may resume treatment with study drug after appropriate treatment of the brain lesion if:
  - Brain lesions are demonstrated to be controlled by gadolinium-enhanced MRI and if patient is neurologically stable within the last 2 weeks prior to the re-initiation of study drug
  - The disease outside of the brain remains controlled prior to re-initiation of study drug. A new tumor assessment will be repeated if the last one available is older than 4 weeks.
  - Time interval between last dose and re-initiation of study drug does not exceed 8 weeks
  - Patient will continue to be followed for safety and efficacy assessments as per schedule of assessment.
- If patient had PD outside of the brain (with minimally symptomatic or no PD in the brain) but still derives clinical benefit from ceritinib following investigator's judgment, patient may continue study drug and continue to be followed for safety and efficacy assessments as per schedule of assessment.

In both cases, all imaging data acquired during tumor assessments conducted after PD has been confirmed by the investigator will continue to be submitted to the designated imaging vendor who will send it to the BIRC for review.

Patients will continue to have scans performed as per protocol (Table 7-1) until investigator's assessed disease progression according to RECIST 1.1 inside the brain, outside the brain or both.

If the patient had PD both intracranially and extracranially but still derives clinical benefit from ceritinib following investigator's judgment, patient may continue study drug and continue to be followed for safety assessments as per schedule of assessment.

7.2.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. For details on AE collection and reporting, refer to Section 8. Significant findings that were present prior to the signing of informed consent must be included in the relevant medical history/current medical conditions 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.

[redacted]

7.2.2.1 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 and, extremities. 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.

7.2.2.2 Vital signs

Vital signs include body temperature, blood pressure 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.

7.2.2.3 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.

7.2.2.4 Performance status

WHO performance status will be assessed as per the assessment schedule (refer to Table 7-1). Assessment of WHO performance status (Table 7-3) will be performed within the time windows described above 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

7.2.2.5 Neurological examination

Baseline neurological examination should evaluate the following:

- General appearance, including posture, motor activity and meningeal signs
- Mini mental status exam (Folstein et al 1975), including speech observation

[redacted]

- Cranial nerves testing from Cranial Nerve II to XII
- Motor system, including muscle atrophy, tone and power
- Sensory system, including position, light touch and sensory function
- Reflexes, including deep tendon reflexes, plantar reflexes
- Coordination (finger-nose testing, dysdiadokinesia, heel-shin testing), gait and Rhomberg test.

The baseline neurological examination will be recorded in the source documentation. 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.

During the conduct of the study, a more basic neurological examination can be conducted to assess the known neurological abnormalities detected at baseline. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

In case of suspicion of neurological deterioration, the complete neurological examination should be conducted and recorded in the source documentation.

7.2.2.6 Laboratory evaluations

Central laboratories will be used for the analysis of scheduled hematology, biochemistry and other blood specimens collected as part of safety monitoring (as detailed in Table 7-1). Dipstick urinalysis will be performed locally (unless local institution policies dictate otherwise), except in the case of any out of range parameter on scheduled local urinalysis, when a urine sample will be sent to central laboratory for further analysis. 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).

The site does not need to wait for the results of centrally-analyzed laboratory assessments when an immediate clinical decision needs to be made and in those cases locally unscheduled testing may be performed.

Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators separately.

[redacted]

Table 7-4 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, 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)
Pregnancy	At screening visit, serum pregnancy test At subsequent cycles, urinary pregnancy test. If local requirements dictate otherwise, local regulations should be followed
Coagulation	Pro-thrombin time (PT) and International normalized ratio [INR]) or Quick Test

7.2.2.6.1 Hematology

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

7.2.2.6.2 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).

7.2.2.6.3 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. In the event this is not allowed per institution or local clinical practice, site must ensure completion, as well as record of rationale for use and results of local lab analysis are available in source documentation and clinical database.

7.2.2.6.4 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.

Women who are determined not to be of child bearing potential before the study will only be tested at screening. 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 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

[redacted]

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 patient must immediately notify the investigator.

Male patients must notify the investigator in case their partner is confirmed with positive pregnancy test results during the treatment period.

7.2.2.6.5 Coagulation

International normalized ratio (INR) and prothrombin time (PT) or Quick Test will be measured at screening only.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as described in Table 7-5.

- At the screening visit in triplicate for all patients and
- At other defined time points as triplicate ECGs for all patients [redacted] (Table 7-5).

Baseline is defined as the pre-dose assessment on Cycle 1 Day 1 before study drug administration.

All ECGs recorded for each time point will be transmitted electronically to a central laboratory and will be centrally reviewed by an independent reviewer in a blinded fashion in regards to time, and day (i.e., Cycle 1 Day 1, Cycle 2 Day 1) identifiers. Any original ECG not transmitted electronically to the central laboratory should be forwarded for central review. Review of all ECGs from a particular patient should be performed by a single reader. The ECG lead for interval duration measurements should be pre-specified. Baseline and all subsequent ECGs should be based on the same lead.

Detailed instructions regarding the ECG collection will be provided to the investigators in a separate manual prior to the start of the study. [redacted] The triplicate ECGs should be taken approximately 2-4 minutes apart.

An ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site.

[redacted]

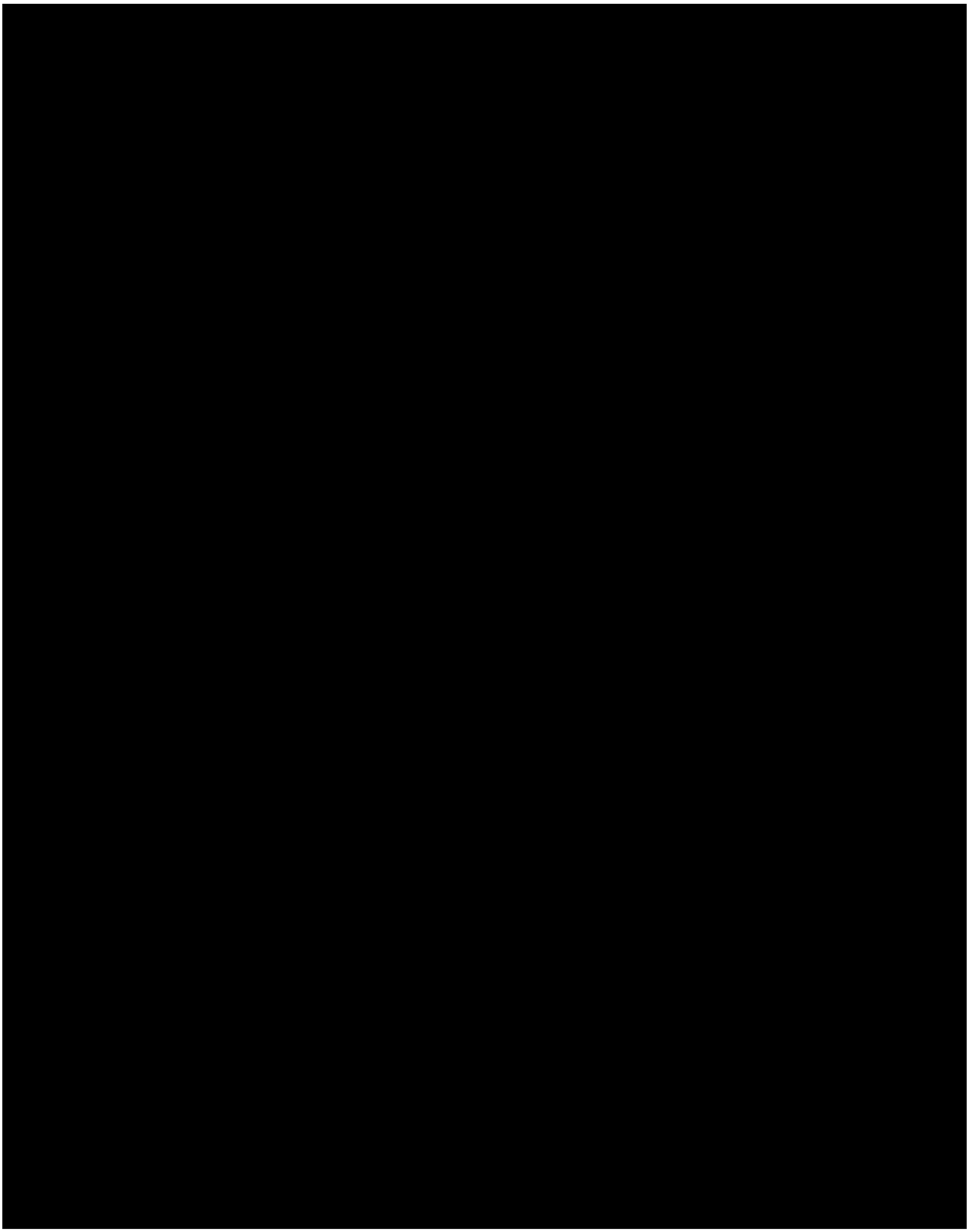
Table 7-5 ECG collection plan for patients [redacted] (triplicate ECGs)

Cycle	Day	Time	ECG Type
Screening	-28 to -1	Anytime	12 Lead
1	1	Predose	12 Lead
1	8	Predose	12 Lead
1	15	Predose	12 Lead
2	1	Predose	12 Lead
2	1	any time between 4 to 10 hr postdose	12 Lead
3	1	Predose	12 Lead
4	1	Predose	12 Lead
5	1	Predose	12 Lead
6	1	Predose	12 Lead
Subsequent cycles and EOT	1	Predose	12 Lead

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]

[redacted]



[redacted]

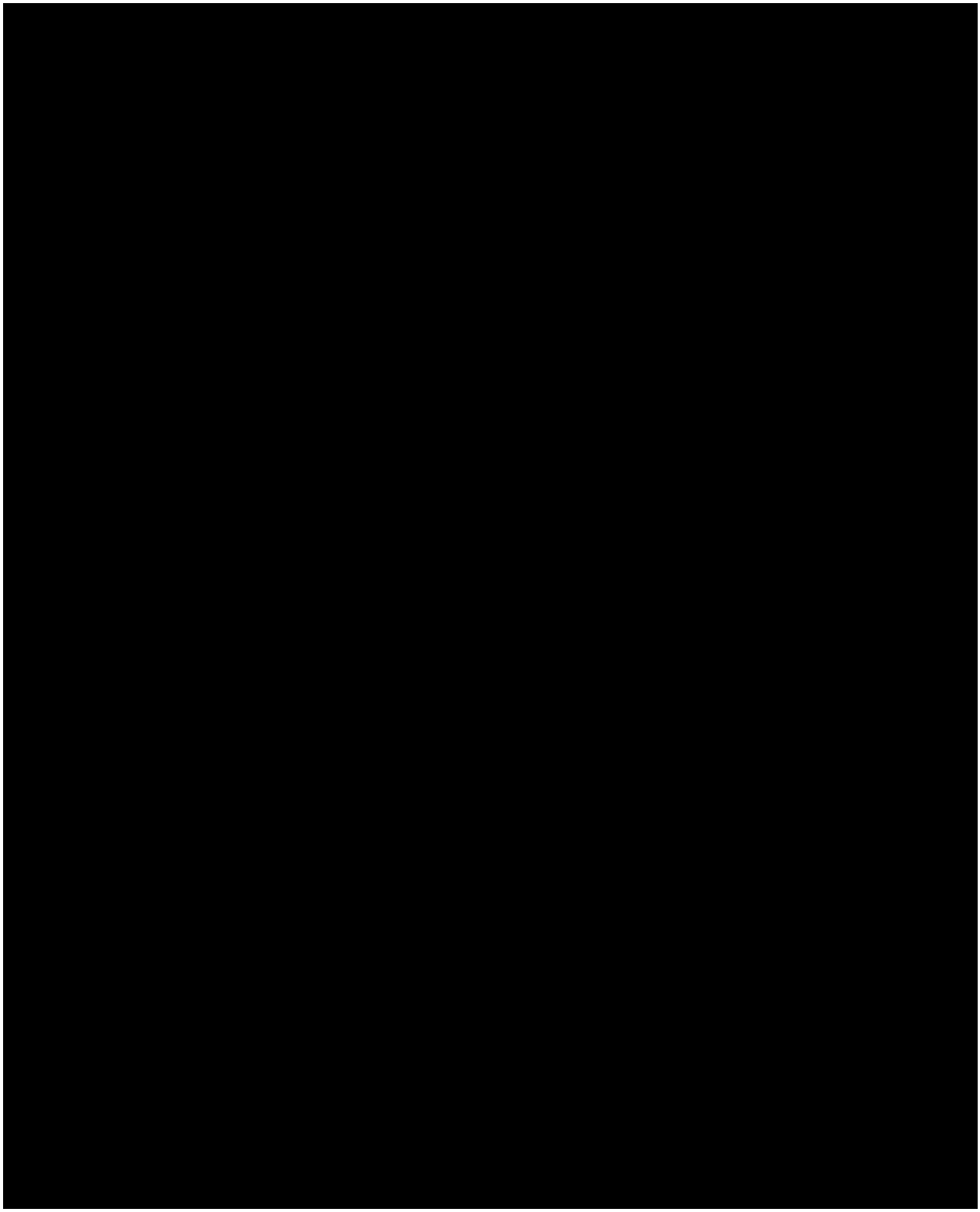
7.2.4 CSF sampling in patients with leptomeningeal carcinomatosis at baseline

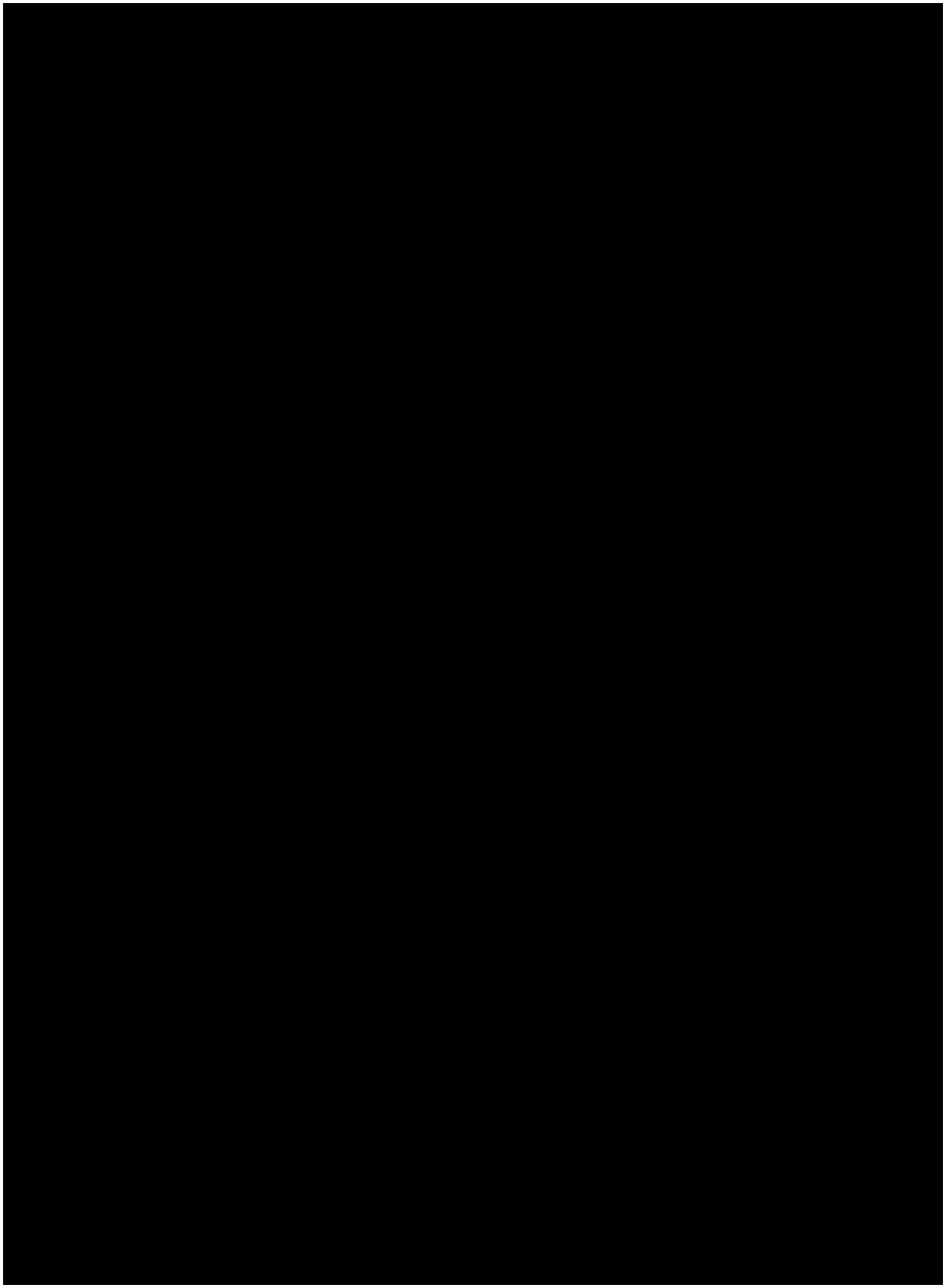
For patients presenting with a baseline leptomeningeal carcinomatosis (LC), diagnosis must be confirmed with documented malignant cells in the cerebrospinal fluid, or if suspected, supported by imaging findings on the Gadolinium-enhanced MRI of the brain or spine (in this latter case, the determination of the presence of malignant cells in CSF cytology is strongly recommended and a CSF sample for cytological evaluation should be taken within the 14 days before initiation of study drug at C1D1). Patients with known and documented positive cytology at screening do not need to be retested. Samples should be obtained from site of disease or initially positive cytology if possible.

During the study CSF will be collected at a frequency determined by local clinical practice unless medically contra-indicated and/or deemed to be an unacceptable burden to patient. The investigator may determine if more frequent evaluations are needed in case of suspected disease progression and/or in accordance with local clinical practice. If there are any signs or radiologic or clinical neurological progression, a CSF will be collected if feasible. Clinical progression may be determined based on results of cytological or neurological evaluations.

Before any CSF collection, the treating physician should rule out any medical condition that would prevent the safe conduct of a lumbar puncture, including but not limited to an increased intracranial pressure, a thrombocytopenia or a bleeding diathesis, an active infection.

[redacted]





[redacted]

7.2.6 Resource utilization

Direct collection of health care resource utilization (HCRU) data related to the treatment of brain metastases will be collected (such as hospitalization, inpatient and outpatient treatment, radiotherapy and radiosurgery).

7.2.7 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.

For patients whose ALK status is unknown and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related to study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event eCRF.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 (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab 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 (dated 14 June 2010). 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 but is collected as seriousness criteria; rather, information about deaths will be collected though a Death eCRF.

[redacted]

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 clinically 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 clinically 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 (subject) 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 (subject) 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:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met

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 CRF.

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 criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

[redacted]

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.

[redacted]

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

[redacted]

- 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

For patients with unknown ALK mutational status and who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g., an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30 days after the last study related procedures.

For patients with known ALK mutational status who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

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 additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes 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.

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.

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 submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE 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, 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

[redacted]

Novartis Chief Medical Office and Patient Safety (CMO&PS) 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.

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 (DMC)

Not applicable.

[redacted]

[redacted]

8.8 Blinded Independent Review Committee (BIRC)

A BIRC will review all the study radiographic and photographic data to determine tumor response and progression. The designated imaging vendor will be responsible for assembling and managing the BIRC. [redacted]

9 Data collection and management

[redacted]

[redacted]

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 eCRFs 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 eCRFs, 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 eCRFs 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 eCRF 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 eCRFs 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.

[redacted]

[redacted]

[redacted]

In addition, data entered into IRT for screening, enrollment/allocation of study treatment, discontinuation, subsequent drug assignment 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]

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, enrollment/allocation of study treatment, subsequent drug assignments and discontinuation
- Central imaging review data (i.e. CT/MRI, Bone scans and photography results)
- Centrally analyzed laboratory data including clinically (chemistry, hematology, coagulation, urinalysis, etc.), [redacted] CSF, blood/tumor biomarker and safety parameters.

[redacted]

- ECG data

Randomization codes and 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. [redacted]

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

10 Statistical methods and data analysis

The data from all participating centers in this protocol will be combined to perform analysis.

Primary analysis of any of the study arms or overall will occur only after enrollment in the specific study arms or overall is complete and all patients have completed at least 24 weeks of treatment with ceritinib or have discontinued earlier respectively. If the end of study criteria is met before the primary analysis is conducted, a single final analysis and study report may be performed. If the end of the study criteria is not met by the time that the primary analysis is conducted, a final CSR will be produced reporting all available data collected up to last patient last visit (LPLV) including the additional study data collected after the primary analysis.

[redacted]

Subsequently, an analysis of all study arms 1 to 5 and overall for all enrolled patients will be performed after the required enrollment in all 5 arms is complete and all treated patients have been followed for at least 24 weeks or have discontinued treatment earlier. Although available data from all study arms will be included in this analysis, this analysis will be considered as primary analysis for all patients and for the study arms not included in the early analysis CSR. For the study arms that were included in the early analysis CSR, the early analysis will be considered as their primary analysis.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) will include all patients who receive at least one dose of ceritinib.

[redacted]

The FAS will be used for summaries of baseline characteristics and all efficacy analyses unless otherwise specified.

10.1.2 Safety Set

The Safety Set will include all patients who receive at least one dose of ceritinib. All safety data will be analyzed using the Safety Set. In this study the FAS and safety set are identical.

10.1.3 Per-Protocol Set

Not applicable.

10.1.4 Dose-determining analysis set

Not applicable.

[redacted]

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by study arm based on the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for the analyses below.

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 received/planned duration), will be listed and summarized by study arm. Dose reductions and dose delays (including the reasons for these) will be listed and summarized by study arm.

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

10.4 Primary objective

The primary objective is to evaluate the antitumor activity of ceritinib in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges.

10.4.1 Variable

The primary variable is the overall response rate (ORR), which is defined as the proportion of patients with a best overall confirmed response of CR or PR in the whole body, as assessed per RECIST 1.1 (Appendix 2) by the investigator.

[redacted]

10.4.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be performed on the FAS. The primary efficacy endpoint ORR will be estimated and the exact 95% confidence interval (CI) provided. ORR will also be summarized by prior radiotherapy to the brain (yes, no), prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4 in the analysis of Arms 1 to 5. Arm 5 will be summarized separately.

10.4.3 Handling of missing values/censoring/discontinuations

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

Patients with a best overall response of "Unknown" per RECIST 1.1 will be considered as non-responders in estimating the ORR.

Descriptive tables displaying missing tumor assessments prior to progression or study discontinuation will be specified in the RAP document.

Patients who have disease progression and continue to receive treatment after progression will qualify for progressive disease at the time of progression and will be counted as PD in ORR and other efficacy endpoint derivations.

[redacted]

10.5 Secondary objectives

[redacted]

10.5.1 Key secondary objective(s)

The key secondary objective is to evaluate Disease Control Rate (DCR). The DCR is defined as the proportion of patients with a best overall response of CR, PR or SD in the whole body, as assessed per RECIST 1.1 by the investigator.

DCR will be estimated and the exact binomial 95% CI will be presented. DCR will also be summarized by prior radiotherapy to the brain (yes, no), prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4. Arm 5 will be summarized separately.

10.5.2 Other secondary efficacy objectives

The following intracranial, extracranial and whole body (for lesions **in and outside** the brain) tumor-response related endpoints (OIRR, IDCR, TTIR, DOIR, OERR, EDCR, TTER, DOER, TTR, DOR and PFS) will be assessed separately based on investigator assessment and BIRC assessment per RECIST 1.1.

All the endpoints described below will be summarized by prior radiotherapy to the brain (yes, no), prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4. Secondary efficacy endpoints will also be summarized using data from Arm 5 separately.

[redacted]

Intracranial endpoints:

Overall intracranial response rate (OIRR): OIRR is calculated based on response assessments in the brain for patients having measurable brain metastases at baseline. The OIRR is defined as the proportion of patients with a best overall confirmed response of CR or PR in the brain as assessed per modified RECIST 1.1. OIRR will be estimated and the exact binomial 95% CI will be presented.

Intracranial disease control rate (IDCR) at 8 and 16 weeks and overall: IDCR is calculated based on response assessments in the brain for patients having evaluable (measurable or non-measurable) brain metastases at baseline. In what follows, CR, PR and SD are possible responses only for patients with measurable brain metastases at baseline, while non-CR/non-PD is a possible response only for patients without measurable brain metastases at baseline.

- The IDCR at 8 and 16 weeks is defined as the proportion of patients with CR, PR, SD or non-CR/non-PD assessment in the brain at Week 8 and Week 16 intracranial tumor evaluations respectively.
- IDCR overall is defined as the proportion of patients with a best overall response of CR, PR, SD or non-CR/non-PD in the brain, as assessed per modified RECIST 1.1 by the investigator.
  IDCR will be estimated and the exact binomial 95% CI will be presented.

Time to intracranial tumor response (TTIR): TTIR is defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) in the brain as assessed per modified RECIST 1.1 criteria for patients with measurable brain metastases at baseline.

The distribution function of TTIR will be estimated using the Kaplan-Meier method. The median TTIR along with 95% CI will be presented.

Duration of intracranial response (DOIR): Among patients with measurable brain metastases at baseline and a confirmed response (PR or CR) in the brain per modified RECIST 1.1, DOIR is defined as the time from the first documented response (PR or CR) in the brain to the date of the first documented disease progression in the brain or death due to any cause. The distribution function of DOIR will be estimated using the Kaplan-Meier method. The median DOIR along with 95% CI will be presented.

Extracranial endpoints:

Overall extracranial response rate (OERR): OERR is defined as the proportion of patients with a best overall confirmed response of CR or PR outside of the brain, as assessed per RECIST 1.1. OERR will be estimated and the exact binomial 95% CI will be presented.

Extracranial disease control rate (EDCR) at 8 and 16 weeks and overall:

- EDCR at 8 and 16 weeks is defined as the proportion of patients with CR, PR or SD outside of the brain at Week 8 and Week 16 extracranial tumor evaluations respectively, as assessed per RECIST 1.1.
- EDCR overall is defined as the proportion of patients with a best overall response of CR, PR or SD outside of the brain as assessed per RECIST 1.1.

[redacted]

EDCR will be estimated and the exact binomial 95% CI will be presented.

Time to extracranial tumor response (TTER): TTER is defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) outside of the brain as assessed per RECIST 1.1 criteria. The distribution function of TTER will be estimated using the Kaplan-Meier method. The median TTER along with 95% CI will be presented.

Duration of extracranial response (DOER): Among patients with a confirmed response (PR or CR) outside of the brain per RECIST 1.1, DOER is defined as the time from the first documented response (PR or CR) outside of the brain to the date of the first documented disease progression outside of the brain or death due to any cause. The distribution function of DOER will be estimated using the Kaplan-Meier method. The median DOER along with 95% CI will be presented.

Whole body endpoints:

ORR by BIRC: The evaluation of ORR will be repeated based on BIRC assessment.

DCR by BIRC: The evaluation of DCR will be repeated based on BIRC assessment.

Time to tumor response (TTR): TTR is defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) in the whole body as assessed per RECIST 1.1 criteria. The distribution function of TTR will be estimated using the Kaplan-Meier method. The median TTR along with 95% CI will be presented.

Duration of response (DOR): Among patients with a confirmed response (PR or CR) in the whole body per RECIST 1.1, DOR is defined as the time from the first documented response (PR or CR) to the date of the first documented disease progression or death due to any cause. The distribution function of DOR will be estimated using Kaplan-Meier method. The median DOR along with 95% CI will be presented.

Progression-free survival (PFS): PFS is defined as the time from the date of the first dose of ceritinib to the date of the first documented disease progression in the whole body per RECIST 1.1 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 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 for any reason 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 for any reason 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. The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% CI will be presented.

Overall survival (OS): OS time is defined as time from the date of first dose of ceritinib to the date of death due to any cause. OS time for patients who are alive at the end of the study or are lost to follow-up will be censored at the date of last contact. OS will be estimated using the Kaplan-Meier method. The median OS along with 95% CI will be presented. Kaplan-

[redacted]

Meier curves will not be produced for Arm 5 alone if the number of patients enrolled in this arm is ≤ 10.

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 study arm and for all patients.

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.

The safety summary tables will include only data collected during the on-treatment period. However, all safety data will be listed with data collected during the pre-treatment and post-treatment period flagged.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs observed 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 pre-treatment and after the on-treatment period will be flagged.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and/ or preferred term, severity (based on CTCAE grades), type of AE, and relation to study treatment by study arm. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and study arm.

Specific safety event categories (SEC) 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.

For each specified category, number and percentage of patients with at least one event per category will be summarized by study arm.

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 (In the unlikely case when a local laboratory normal range overlaps into the higher (i.e. non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero.). 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.

[redacted]

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary 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 will be generated.

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

[redacted]

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 the RAP document.

10.5.3.5 Tolerability

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

[redacted]

[redacted]

10.5.5.2 Data handling principles

Not applicable

10.5.5.3 Data analysis principles

10.5.5.3.1 Analysis sets

[redacted], all statistical analyses of biomarker data will be performed on patients with biomarker data.

[redacted]

[redacted]

10.5.5.3.3 Advanced analysis methods

Not applicable

10.6 Exploratory objectives

RANO exploratory objectives

Exploratory analyses will be conducted to evaluate intracranial endpoints by investigator and BIRC including OIRR, TTIR, DOIR for patients with measurable brain metastases at baseline, and IDCR for all patients in Arms 1 to 4 with active brain lesion at baseline using Response Assessment in Neuro-Oncology (RANO) criteria for high grade gliomas (Appendix 3).

[redacted]

10.8 Sample size calculation

The study will enroll approximately 160 patients, with approximately 40 patients each in Arms 1 and 2 and ~30 patients each in Arms 3 and 4 and at least 20 patients in Arm 5 (See Table 2-1). It is assumed that 5% of the patients diagnosed with brain metastases have leptomeningeal carcinomatosis. Additional patients in Arm 4 may be enrolled in order achieve approximately 60 patients in Arms 3 and 4 together (i.e. ALKi naïve patients) if enrollment rate in Arm 3 is slow.

An observed ORR of 50% in 140 patients planned for Arms 1-4 will result in an exact binomial 95% CI with a lower bound greater than 40% which is clinically meaningful and exceeds the ORR expected with available therapies (Shaw 2012). Table 10-1 provides the exact binomial 95% CI for various observed ORRs for the 140 patients and for each of the strata.

Table 10-1 Exact binomial 95% confidence intervals for various observed ORRs

Sample Size	Observed ORR	Number of Patients with Confirmed PR or CR	Exact 95% CI
N=140 (overall Arms 1-4)	50%	70	(41.44%, 58.56%)
	60%	84	(51.39%, 68.18%)
N=80 (Arms 1 and 2)	40%	32	(29.20%, 51.56%)
	50%	40	(38.60%, 61.40%)
	60%	48	(48.44%, 70.80%)
N=40 (each of Arms 1 or 2)	40%	16	(24.87%, 56.67%)
	50%	20	(33.80%, 66.20%)
N=30 (each of Arms 3 or 4)	60%	18	(40.60%, 77.34%)
	70%	21	(50.60%, 85.27%)

10.9 Power for analysis of key secondary variables

Estimation of the DCR is the key secondary objective of the study. An observed DCR of 65% in 140 patients in Arms 1-4 will result in an exact binomial 95% CI with a lower bounder greater than 55%. Table 10-2 provides the exact binomial 95% CI for various observed DCRs for the 140 patients and for each of the strata.

Table 10-2 Exact binomial 95% confidence intervals for various observed DCRs

Sample Size	Observed DCR	Number of Patients with SD, PR or CR	Exact 95% CI
N=140 (overall Arms 1-4)	65%	91	(56.49%, 72.86%)
	75%	105	(66.98%, 81.93%)
N=80 (Arms 1 and 2)	60%	48	(48.44%, 70.80%)
	70%	56	(58.72%, 79.74%)
N=40 (each of Arms 1 or 2)	60%	24	(43.33%, 75.14%)
	70%	28	(53.47%, 83.44%)
N=30 (each of Arms 3 or 4)	70%	21	(50.60%, 85.27%)
	80%	24	(61.43%, 92.29%)

[redacted]

An additional secondary objective of the study is estimation of the OIRR for patients with measurable brain metastases at baseline. As described in Section 4.1.1, the study targets enrolling approximately 70 patients with measurable brain metastases: ~50 patients with prior ALKi treatment (Arms 1 and 2) and ~20 patients with no prior ALKi treatment (Arms 3 and 4). An observed OIRR of 50% in 70 patients with measurable brain metastases in Arms 1-4 will result in an exact binomial 95% CI with a lower bound greater than 35%. An observed OIRR of 60% in 50 patients with measurable brain metastases previously treated with and ALKi (Arms 1 and 2) will result in an exact binomial 95% CI with a lower bound greater than 45%. An observed OIRR of 60% in 20 patients with measurable brain metastases not previously treated with and ALKi (Arms 3 and 4) will result in an exact binomial 95% CI with a lower bound greater than 36%. The reported OIRR with Crizotinib is 18% (95% CI: 5 - 40) for patients with measurable brain metastases and prior radiation therapy to the brain, and 33% (95% CI: 13 - 59) for patients without prior radiation to the brain; recent whole brain radiation was allowed (Crino et al 2013).

Table 10-3 Exact binomial 95% confidence intervals for various observed OIRRs

	Observed OIRR	Number of Patients with Confirmed PR or CR in the brain	Exact 95% CI
N=70 (Overall Arms 1-4)	45%	32	(33.74%, 58.06%)
	50%	35	(37.80%, 62.20%)
	55%	39	(43.34%, 67.59%)
	60%	42	(47.59%, 71.53%)
N=50 (prior ALKi treatment, Arms 1+2)	40%	20	(26.41 %, 54.82 %)
	45%	23	(31.81 %, 60.68 %)
	50%	25	(35.53%, 64.47%)
	55%	28	(41.25%, 70.01%)
	60%	30	(45.18%, 73.59%)
N=20 (no prior ALKi treatment, Arms 3+4)	50%	10	(27.20%, 72.80%)
	55%	11	(31.53%, 76.94%)
	60%	12	(36.05%, 80.88%)
	65%	13	(40.78%, 84.61%)

11 Ethical considerations and administrative procedures

11.1 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.

11.2 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

[redacted]

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.

11.3 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 eCRFs.

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.

[redacted]

11.4 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.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on

[redacted]

www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis followed the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publications will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 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 (eCRF) 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 eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. Any change or correction to a paper eCRF should be dated, initialed, and explained (if necessary) and should not obscure the

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original entry. For electronic eCRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper eCRFs.

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.

11.7 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.

11.8 Audits and inspections

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

11.9 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

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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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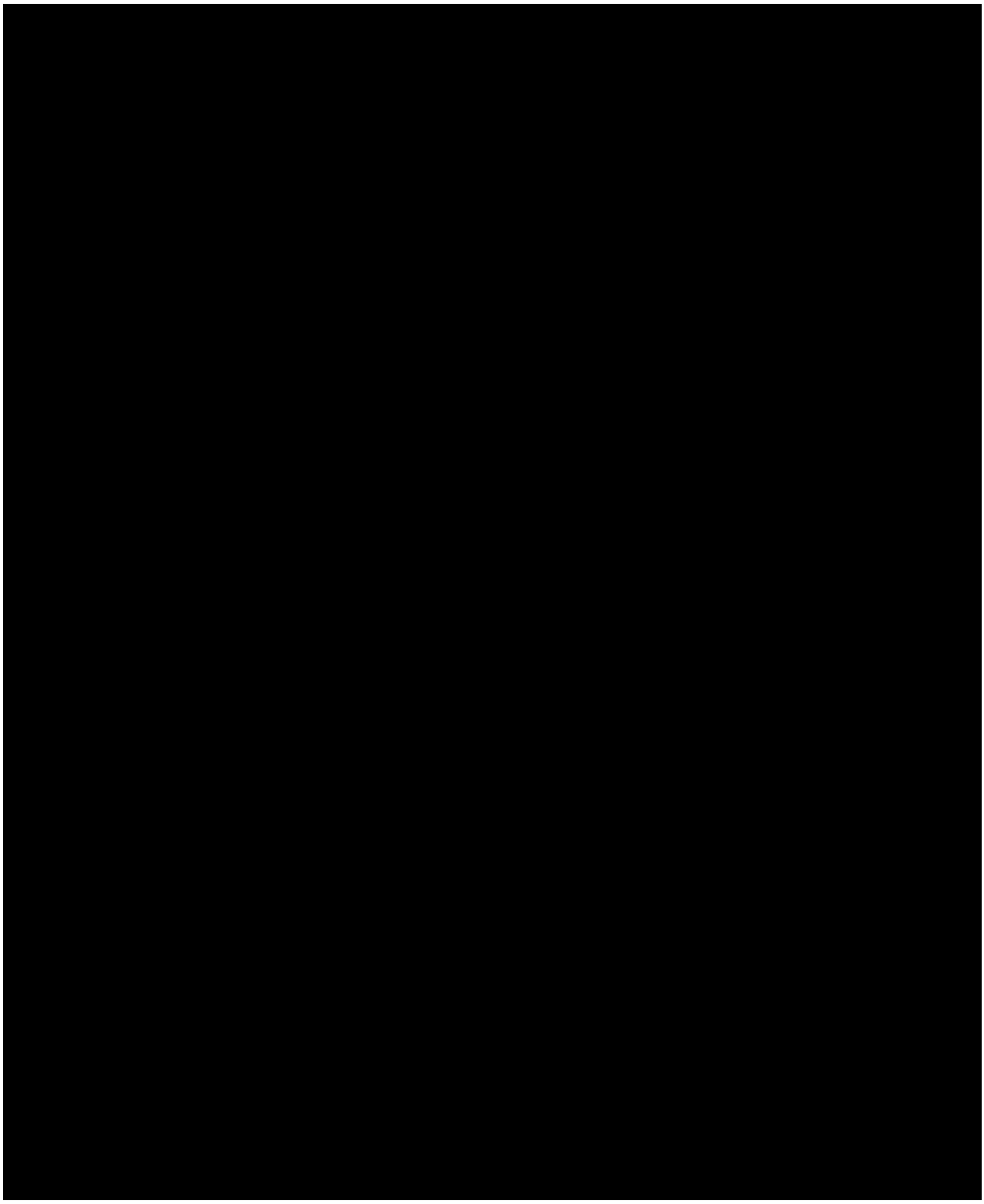
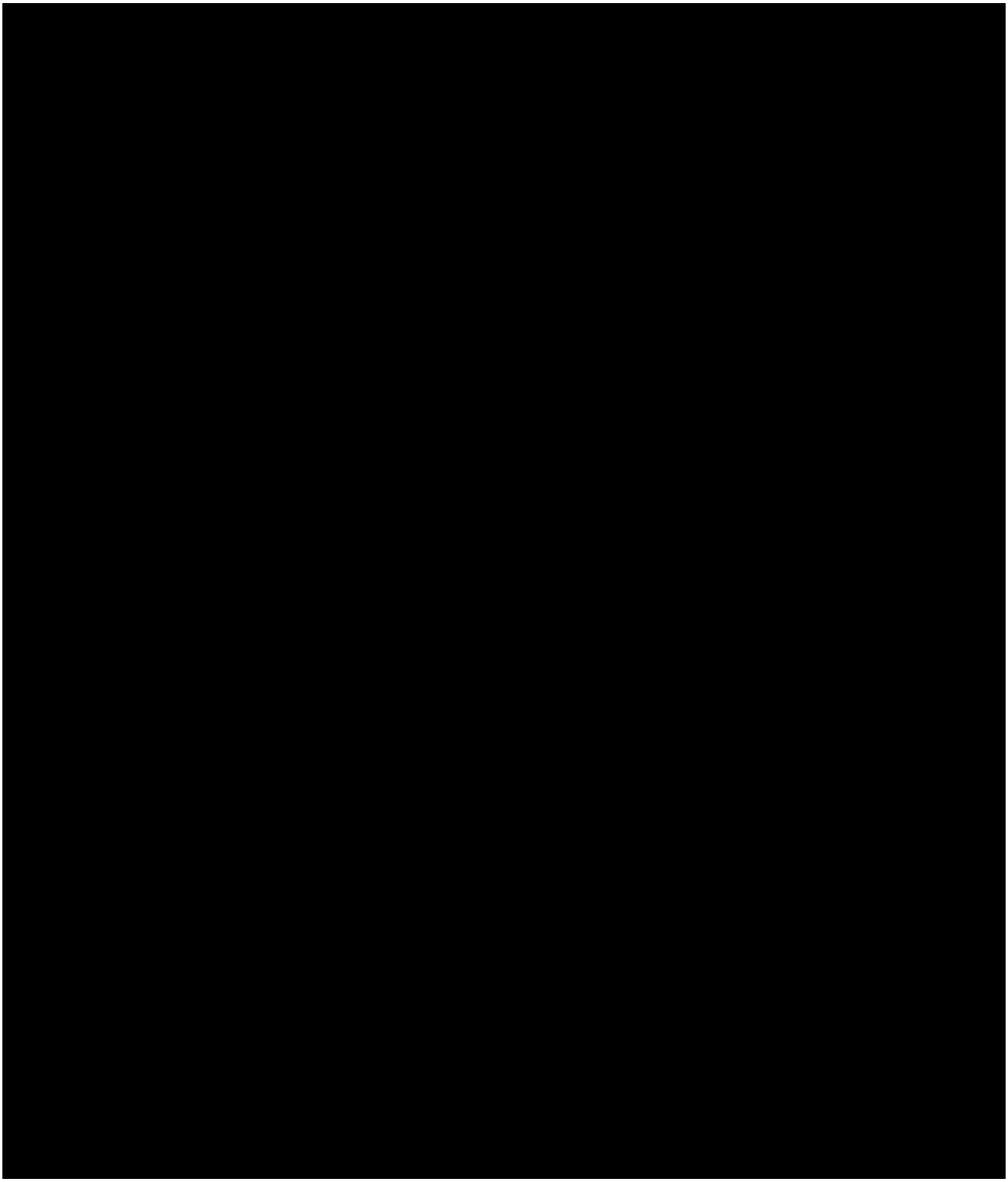
14 Appendices





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

Guidelines for Response, Duration of Overall Response, TTF, TTP, PFS and Overall Survival (based on RECIST 1.1)

Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

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14.2.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 14.2.2 and the definition of best response in Section 14.2.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.2.18 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.2.28 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.2.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

14.2.3 Definitions

14.2.4 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.2.26.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

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- **Cystic lesions:**
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.2.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.2.26.

14.2.6 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm 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 baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication 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.

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- 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 result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET:** can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with 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 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 CT 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.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound:** When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy:** The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers:** Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions

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and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

- **Clinical examination:** Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.2.7 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions:** All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.2.4.
- **Nodal target:** See Section 14.2.4.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions:** All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

14.2.8 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately

[redacted]

for the target (Table 14-5) and non-target lesions (Table 14-6) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-7) as well as the presence or absence of new lesions.

14.2.9 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

14.2.10 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.2.11 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a “non-zero size” will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

[redacted]

14.2.12 Determination of target lesion response

Table 14-5 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of 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[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1]. SOD for CR may not be zero when nodal lesions are part of target lesions
[2]. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3]. Methodology change See Section 14.2.6.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-5 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements:** In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However,

[redacted]

in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- **Nodal lesion decrease to normal size:** When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split:** In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced:** Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
    - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
    - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
    - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

14.2.13 Determination of non-target lesion response

Table 14-6 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1]. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- **Unequivocal progression:** To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.2.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.2.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- 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.

[redacted]

- 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 (see Section 14.2.15).
- 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.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.2.6.

14.2.15 Evaluation of overall lesion 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 shown below in Table 14-7.

Table 14-7 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1]. This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2]. Once confirmed PR was achieved, all these assessments are considered PR.
[3]. As defined in Section 14.2.8.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

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

14.2.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.2.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

[redacted]

14.2.17 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status

[redacted]

other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

[redacted]

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.2.18 Time to event variables

The protocol should state which of the following variables is used in that study.

14.2.19 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

14.2.20 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

14.2.21 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

[redacted]

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.2.22 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.2.23 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

14.2.24 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.2.23. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

14.2.25 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the

[redacted]

assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.2.26).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

14.2.26 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies

[redacted]

with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-8.

Table 14-8 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 14.2.8.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

14.2.27 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

[redacted]

Based on definitions outlined in Section 14.2.25, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics-April 2005) as a reference, the following analyses can be considered:

Table 14-9 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two** or more missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1].=Definitions can be found in Section 14.2.25.
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.2.25.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

[redacted]

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-9 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.2.28 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

14.2.29 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.2.30 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee 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.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

14.2.31 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

14.2.32 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK)

[redacted]

and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.2.33 Programming rules

The following should be used for programming of efficacy results:

14.2.34 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

14.2.35 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.2.25). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

14.2.36 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

[redacted]

14.2.37 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered ‘not applicable (NA)’.

14.2.38 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

[redacted]

[redacted]

14.2.40 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791.

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47.

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465.

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18.

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16.

[redacted]

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

[redacted]

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

14.3.5.2 Performance status

Participants will be graded according to KPS score

[redacted]

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: Cockcroft-Gault formula

Female:

$$GFR[ml/\min] = 0.85 \cdot \frac{(140 - age[y]) \cdot bodyweight[kg]}{72 \cdot serum\ creatinine\ [mg/dl]}$$

Male:

$$GFR[ml/\min] = \frac{(140 - age[y]) \cdot bodyweight[kg]}{72 \cdot serum\ creatinine\ [mg/dl]}$$

[redacted]