NOVARTIS

Clinical Development

Ceritinib (LDK378)

Protocol CLDK378AUS23 / NCT02186821

# Modular phase II study to link targeted therapy to patients with pathway activated tumors: Module 7 – Ceritinib (LDK378) for patients whose tumors have aberrations in ALK or ROS1

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## List of abbreviations

| | |
|---|---|
| ADME | Absorption Distribution Metabolism and Excretion |
| AE | Adverse Event |
| AKT | Protein Kinase B |
| ALCL | Anaplastic Large Cell Lymphoma |
| ALL | Acute lymphoblastic leukemia |
| ALT | Alanine aminotransferase/glutamic pyruvic transaminase/GPT |
| AML | Acute myelogenous leukemia |
| ANC | Absolute Neutrophil Count |
| AP | Alkaline Phosphatase |
| APL | Acute promyelcytic leukemia |
| aPTT | Activated partial thromboplastin time |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC0-24h | Area Under the Curve 0-24 h |
| BID | bis in diem/twice a day |
| BLRM | Bayesian Logistic Regression Model |
| BP | Blood pressure |
| BRAF/B-Raf | v-raf murine sarcoma viral oncogene homolog B1 |
| BSC | Best supportive care |
| BUN | Blood Urea Nitrogen |
| Ca | Calcium |
| CA-125 | Cancer Antigen-125 |
| CABG | Coronary artery bypass graft |
| CBC | Complete blood count |
| CBR | Clinical benefit rate |
| [redacted] | [redacted] |
| CFR | Code of Federal Regulations |
| CHF | Congestive heart failure |
| CI | Confidence Interval |
| CL | Clearance |
| CLIA | Clinical Laboratory Improvement Amendments |
| CLL | Chronic lymphocytic leukemia |
| Cmax | Maximum Concentration |
| CML | Chronic Myeloid Leukemia |
| CNS | Central Nervous System |
| CPK | Creatine phosphokinase |
| CR | Complete Response |
| CRC | Colorectal Cancer |
| CrCl | Creatinine clearance |
| CRO | Contract Research Organization |
| CSF | Clinical service form |
| CSR | Clinical study report |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |

| | |
|---|---|
| CVA | Cerebrovascular accident |
| CYP | Cytochrome P |
| DILI | Drug Induced Liver Injury |
| DLs | dose levels |
| DLT | Dose Limiting Toxicity |
| DNA | Deoxyribonucleic Acid |
| DOR | Duration of Response |
| DS&E | Drug Safety & Epidemiology |
| DVT | Deep vein thrombosis |
| e.g. | for example |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report/Record Form |
| EDC | Electronic Data Capture |
| EGF | Epidermal growth factor |
| EGFR | Epidermal growth factor receptor |
| ET | Essential thrombocythemia |
| EOT | End of Treatment |
| ERK/MAPK | Extracellular signal-regulated kinase/Mitogen-Activated Protein Kinase |
| EU | European Union |
| FDA | Food and Drug Administration |
| FAS | Full Analysis Set |
| FDG-PET | Fluorodeoxyglucose-Positron Emission Tomography |
| FFPE | Formalin fixed paraffin embedded |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| G-CSF | granulocyte colony stimulating factor |
| GGT | Gamma-glutamyltranspeptidase |
| GI | Gastrointestinal |
| GLP | Good laboratory practice |
| GM-CSF | Granulocyte macrophage colony-stimulating factor |
| GVHD | Graft-versus-host disease |
| HBV | Hepatitis B Virus |
| hCG | human chorionic gonadotropin |
| HCV | Hepatitis C Virus |
| HDL | High density lipoprotein |
| hERG | human Ether-à-go-go Related Gene |
| HFSR | Hand and Foot Skin Reaction |
| Hgb | Hemoglobin |
| HIV | Human immunodeficiency virus |
| hr | hour |
| IB | Investigators Brochure |
| IC50 | Half maximal Inhibitory Concentration |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |

| | |
|---|---|
| ILD | Interstitial Lung Disease |
| IMWG | International Myeloma Working Group |
| IN | Investigator notification |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IUD | intrauterine device |
| IUS | intrauterine system |
| IWG | International working group |
| KA | Keratoacanthoma |
| KRAS | V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog |
| LDH | Lactate dehydrogenase |
| LDL | Low density lipoprotein |
| LVEF | Left Ventricular Ejection Fraction |
| MAA | Marketing Authorization Application |
| mCRC | Metastatic Colorectal Cancer |
| MDS | Myelodysplasia |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MF | Myelofribrosis |
| MEK | Mitogen-activated ERK Kinase |
| mg | milligram |
| MI | Myocardial infarction |
| MM | Multiple Myeloma |
| MRI | Magnetic Resonance Imaging |
| MTD | Maximum Tolerated Dose |
| mTOR | Mammalian target of rapamycin |
| MUGA | Multiple Gated acquisition scan |
| N | Sample size |
| NA | Not applicable |
| Na | Sodium |
| NCCN | National Comprehensive Cancer Network |
| NCI CTC | National Cancer Institute Common Terminology Criteria |
| nM | Nano molar |
| NSCLC | Non-small cell lung carcinoma |
| OC | Oral contraception |
| OR | Overall response |
| ORR | Overall Response Rate |
| OS | Overall survival |
| PD | Progressive disease |
| PD | Pharmacodynamics |
| PE | Pulmonary embolism |
| PET | Positron emission tomography |
| PFS | Progression-free survival |
| Ph | Philadelphia chromosome |
| PHI | Protected health information |
| PK | Pharmacokinetics |
| PLT | Platelets |
| PR | Partial Response |

| | |
|---|---|
| PRBC | Packed Red Blood Cells |
| PSA | Prostate-specific antigen |
| PT | Prothrombin time |
| PTEN | Phosphatase and tensin homolog |
| PV | Polycythemia vera |
| QD | *quaque die*/once a day |
| QTc | QT corrected |
| QTcF | Q-T interval in the ECG (corrected according to the formula of Fridericia) |
| R Value | ALT/ALP in x ULN |
| RAF | v-raf murine sarcoma viral oncogene |
| RAP | Reporting Analysis Plan |
| RAS | RAS oncogene (rat sarcoma viral oncogene homologue) |
| RBC | Red Blood Cells |
| REB | Research Ethics Board |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| RP2D | Recommended phase two dose |
| RTK | Receptor tyrosine kinase |
| RU | Resource utilization |
| SAE | Serious Adverse Event |
| SBP | Systolic blood pressure |
| SC | Steering Committee |
| SCC | Squamous cell carcinoma |
| SD | Stable disease |
| SGOT | Serum glutamic oxaloacetic transaminase/AST |
| SGPT | Serum glutamic pyruvic transaminase/ALT |
| SPEP | Serum protein electrophoresis |
| SUSAR | Suspected unexpected serious adverse reaction |
| TBIL | Total bilirubin |
| TdP | Torsade de Pointes |
| TIA | Transient ischemic attack |
| Tmax | The time at which the maximum observed concentration (Cmax) occurs |
| TSH | Thyroid stimulating hormone |
| ULN | Upper Limit of Normal |
| UPEP | Urine protein electrophoresis |
| WBC | White Blood Cell |
| WHO | World Health Organization |
| WNL | Within normal limits |

## Glossary of terms

| | |
|---|---|
| Assessment | A procedure used to generate data required by the study |
| Cycles | Number and timing or recommended repetitions of therapy are usually expressed as number of days. For this protocol, a complete treatment cycle is defined as 28 days of once daily continuous treatment with ceritinib. The first dose of ceritinib defines Day 1 of the treatment cycle and the last day of a complete treatment cycle is Day 28, unless extended due to adverse events. |
| Baseline | Pre-dose Cycle 1 day 1 |
| Dose level | The dose of drug given to the patient (total daily or weekly etc.) |
| Enrollment | Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol) |
| Investigational drug | The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug”. Ceritinib is the investigational drug in this study |
| 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. Ceritinib is the investigational treatment. |
| Patient Number (Patient No.) | A unique identifying number assigned to each patient who enrolls in the study |
| Premature patient withdrawal | Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival |
| Screening | Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol) |
| Stage related to study timeline | A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, completion of treatment, etc. |
| Stage in cancer | The extent of 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 treatment was discontinued whichever is later |
| Study treatment | Ceritinib |
| Study treatment discontinuation | Point/time when patient permanently stops taking ceritinib, for any reason |
| Variable | Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points |

# Amendment 2

## Amendment rationale

This amendment provides follow-up evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases in order to optimize the patient safety. Other changes were implemented in this amendment:

- Exclusion criteria for contraception use is being updated to reflect the current guidance.
- Additional exclusion criteria to exclude patients with a history of carcinomatous meningitis.
- Addition of dose modification guidance for QTcF text was updated to provide clarification on monitoring procedures.
- Other general modifications to study language to maintain consistency with standard core protocol language for ceritinib clinical studies.

## Changes to the protocol

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

The following changes were implemented throughout the protocol:

List of study authors was updated.

List of abbreviations was updated to include the terms DILI (Drug Induced Liver Injury), TBIL (Total bilirubin), and R Value (ALT/ALP in x ULN).

Section 1.2.1 “Overview of ceritinib” revised to include updated approval information for Zykadia.

Section 5.3 “Exclusion criteria” includes an additional exclusion criteria for patients with a history of carcinomatous meningitis.

Section 5.3 “Exclusion criteria” includes revised pregnancy language

**Old language**: Combination of the following (a+b or a+c, or b+c):

a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

**New language**: 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.

Section 6.3.3 “Criteria for interruption and re-initiation of ceritinib treatment has been revised to include new language for continuation of treatment for patients ongoing at the time of data cutoff for the CSR.

Table 6-3 “Ceritinib related toxicity management guidelines” includes revised language for electrocardiogram QT corrected (QTc) interval prolonged.

Section 6.3.4.2 “Guidelines for follow-up of laboratory liver abnormalities” has been revised to include guidelines for DILI cases.

Additional minor editorial corrections have been made throughout the protocol.

## IRB/IEC Approval

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.

## Amendment 1

### Amendment rationale

The main purpose of this protocol amendment is to incorporate updates 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 additional dose modification and follow up monitoring language for patients who may experience this safety finding.

Appendix Q "Bayesian Adaptive Design" was revised. In a single arm trial without a control arm, the quality of the inferences depend strongly on historical data used to create a credible estimate of the baseline control rate. For this and other trials within Novartis's Modular phase II program, this required an estimate of the patient population that would be enrolled. A control estimate was initially formed for each group based on that population estimate. As enrollment progressed, a different patient population was enrolled in terms of previous line of therapy exposure (heavily pretreated). In order to produce the best inferences for future development decisions, it is important to change the assumed baseline control rates to match the population enrolled in the program, rather than relying on the pre-trial assumptions. Previously this section was tailored to the CLDK378AUS23 trial. The revised appendix will be used for all trials within Novartis's Modular phase II program. The purpose of this section is to show how Bayesian adaptive design will be used for the analysis of the primary efficacy endpoint. Each trial will be analyzed according to the tumor cohorts that will be formed during the course of the study.

Additional changes include the possible discontinuation of survival follow-up if the primary endpoint of the study is not met, a revised definition for "End of Study" to clarify when data will be reported, and language modifications to maintain consistency with standard core protocol language for ceritinib clinical studies.

### Changes to the protocol

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

The following changes were implemented throughout the protocol:

List of study authors was updated.

[redacted]

Protocol Summary “Purpose and rationale”, “Study design” and “Inclusion criteria”, Section 2.2 “Rationale for the study design”, Section 4.1 “Description of study design”, Section 5.1 “Patient population”, and Section 5.2 “Inclusion criteria” removed the word “select”.

Protocol summary “Study Design” and “Efficacy assessments”, Section 4.1.2 “Follow-up phase”, Section 7.1.4.3 “Survival Follow-up”, Section 10.5.2 “Other secondary efficacy objectives” was changed to clarify that survival follow up may be discontinued if the primary endpoint of the study is not met.

Protocol Summary “Study design” and Section 7.1.1 “Screening” have been revised to clarify that laboratory results from genomic profiling must be ‘unambiguous’ or ‘unequivocal’. Results that state ‘ambiguous’ or ‘equivocal’ imply low probability that genetic deregulation is truly present and an important driver of patient’s tumor.

Section 2.1 “Study rationale and purpose”, Table 7-1, [redacted]

Changes to the inclusion/exclusion criteria (Protocol summary and Sections 5.2 and 5.3):

- Additional inclusion criteria for alkaline phosphatase (≤ 5.0 x ULN) and fasting plasma glucose (≤ 175 mg/dL (≤ 9.8 mmol/L).
- Clarified that calcium should be corrected for serum albumin, not phosphorus.
- Revised inclusion criteria for platelets, hemoglobin, serum creatinine, AST/ALT, and serum bilirubin.
- Additional exclusion criteria for patients with a history of carcinomatous meningitis.
- Revised exclusion criteria for patients with pancreatitis, cardiac function, severe acute or chronic medical conditions, radiotherapy, and major surgery.

Section 1.2.1 “Overview of ceritinib” was revised to include information about marketing authorization applications for Zykadia.

Section 1.2.3 “Non-clinical experience” includes new preclinical data.

Section 1.2.4 “Clinical experience” and Table 1-1 includes new information regarding the incidence of grade 3-4 AEs.

Section 1.2.4 “Clinical experience” includes removal of ECG data.

Section 1.2.4.1.1 “Clinical efficacy” now includes data for PFS based on investigator assessment, and data on ceritinib activity in patients with brain metastases. Additionally, Tables 1-3, 1-4, and 1-5 were removed.

Section 1.2.4.1.2 “Clinical pharmacokinetics” was revised to expand upon the low-fat and high-fat meals, and to include the results of a food effect assessment.

Section 1.3 “Risk and Benefits” was added to include an evaluation of the anticipated benefits and risks of ceritinib to comply with EU clinical trial regulations.

Section 4.2 “Definition of end of the study” was revised to include information regarding the analysis of study data and the CSR.

Section 6.3 “Dose modifications” includes a new section entitled: General guidelines for dose modifications for toxicities other than those listed in Table 6-3. Also included are revisions to the “Permitted study treatment adjustments for ceritinib” and “Criteria for interruption and re-initiation of ceritinib treatment” sections.

Table 6-3 was revised to include a Pancreatic section, updates to the Renal section (serum creatinine), a change to the Metabolic section (persistent hyperglycemia), and changes to the Cardiac section (Electrocardiogram QT corrected interval prolonged).

Section 6.3.4 “Follow-up for toxicities” includes a new sentence (An unscheduled visit should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments). Additionally, modifications were made to the guidelines for the follow-up of laboratory hematologic abnormalities, laboratory liver abnormalities, and laboratory renal abnormalities sections.

Section 6.3.4.8 “Guidelines for the follow-up of laboratory pancreatic abnormalities” has been added.

Table 6-4 includes revisions to the time points for monitoring toxicities, and includes a new section for pancreatic investigations.

Section 6.4 “Concomitant medications” includes revisions to the language for medications that need to be recorded on the eCRF.

Section 6.4.1.1 “Bisphosphonates” has been revised to include a statement about drug-drug interaction.

Section 6.4.2.1 “Corticosteroids” has been modified.

Section 6.4.2.2 “Drugs that are metabolized by CYP450 enzymes” was revised to clarify that strong “inhibitors or” inducers of CYP3A4/5 is prohibited.

Section 6.4.2.4 “Palliative radiotherapy and surgery” includes the removal of “BIRC confirmed” for progressive disease.

Section 6.4.3.1 “Other investigational and anti-neoplastic therapies” now includes “targeted therapy”.

Section 6.4.3.2 “Warfarin and coumadin derivatives” was updated to clarify that “therapeutic doses of “ warfarin sodium or any other coumadin-derived anticoagulants are not permitted.

Section 7.1.1 “Screening” includes a new statement about when archival or fresh tumor samples may not be required for patients.

Section 7.2.1.1 “Solid Tumors” and Section 10.4 “Primary objective” were updated to clarify that if the assessment of CR or PR evaluated 4 weeks after the initial observation differ, then the best overall response will be determined as outlined in Appendix B.

Section 7.2.1.2.4 “Bone marrow assessment” includes the addition of a bone marrow aspirate.

[redacted]

Section 8.2 “Adverse events of special interest” includes new AEs.

Section 10.4.3 “Evaluation of trial success and futility” was revised to include an additional CBR evaluation after database lock for the primary CSR.

Section 10.5 1 “Key secondary objective(s)” was revised to include assessment of Complete Response.

Section 10.5.2 “Other secondary efficacy objectives” was revised.

[redacted]

Section 10.7 “Interim analysis” has been revised.

Section 10.8 “Sample size calculation has been revised.

Appendix A: Criteria for therapeutic response/outcome assessment of solid tumors and/or lymph nodes” has been revised.

Appendix Q “Bayesian Adaptive Design” has been revised.

Additional minor editorial corrections have been made throughout the protocol.

## IRB/IEC Approval

- 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.

## Protocol summary

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|---|---|
| **Protocol number** | CLDK378AUS23 |
| **Title** | Modular phase II study to link targeted therapy to patients with pathway activated tumors: Module - 7 Ceritinib (LDK378) for patients whose tumors have aberrations in ALK or ROS1 |
| **Brief title** | Ceritinib (LDK378) for patients whose tumors have aberrations in ALK or ROS1 |
| **Sponsor and Clinical Phase** | Novartis<br>Phase II |
| **Investigation type** | Drug |
| **Study type** | Interventional |
| **Purpose and rationale** | The purpose of this signal seeking study is to determine whether treatment with ceritinib demonstrates sufficient efficacy in pathway-activated solid tumors and/or hematologic malignancies to warrant further study. |
| **Primary Objective(s) and Key Secondary Objective** | **Primary objectives**:<br>To assess clinical benefit associated with ceritinib treatment based on local investigator assessment<br><br>For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR or PR or SD ≥ 16 weeks. For hematologic tumors, other appropriate hematological response criteria will apply and are included in the appendices<br><br>**Key Secondary objective**:<br>To assess Overall Response (OR) of Partial Response (PR) or greater based on local investigator assessment<br><br>For patients with solid tumors, the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For hematologic tumors, other appropriate hematological response criteria will apply and are included in the appendices. |
| **Secondary Objectives** | **To assess**:<br>Progression-Free Survival (PFS) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria<br><br>Overall Survival (OS)<br><br>Duration of Response (DOR) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria<br><br>Safety and tolerability |
| [redacted] | |
| **Study design** | This is a phase II, open label study to determine the efficacy and safety of treatment with ceritinib in patients with a diagnosis of solid tumors or hematological malignancies that have been pre-identified (prior to study consent) to have ALK or ROS1 positive mutations, translocations, rearrangements or amplifications and whose disease has progressed on or after standard treatment.<br><br>Genomic profiling is becoming more accessible to patients and their physicians. As such, more patients have been identified with potentially-actionable genomic alterations or pathway-activations but do not have access to targeted drug treatment. This is a signal seeking study to match patients with tumors containing ALK or ROS1 positive |

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| | mutations, translocations, rearrangements or amplifications to treatment with the ALK kinase inhibitor ceritinib. Pre-identification of ALK or ROS1 positive mutation, translocation, rearrangement or amplification status will be performed locally at a CLIA certified laboratory prior to participation on the trial. Laboratory results must be 'unambiguous' or 'unequivocal'. Results that state 'ambiguous' or 'equivocal' imply low probability that genetic deregulation is truly present and an important driver of patient's tumor.<br><br>Once the patient has been identified, treating physicians who are qualified investigators may contact Novartis to consider enrollment in this study. For the purpose of this study, genomic profiling is not considered part of screening. Informed consent must be signed before any screening activities take place. Once eligibility (screening criteria met) has been confirmed by Novartis, the patient will initiate therapy with ceritinib single-agent. The patient may not receive any additional anti-cancer therapy during treatment with ceritinib.<br><br>Patients will continue to receive study treatment until disease progression (assessed by investigator per RECIST 1.1 or appropriate hematologic response criteria), unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator), otherwise known as End of Treatment. All patients who discontinue from study treatment due to disease progression must have their progression clearly documented.<br><br>Disease assessment (per RECIST 1.1 or appropriate hematological response criteria) will be performed every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle), until disease progression or end of treatment, whichever occurs first. The frequency of disease assessment may be reduced to every 12 weeks for patients who have at least 4 post-baseline disease assessments and are clinically stable (except MM and AML patients). Scans will be assessed locally by the investigator.<br><br>After discontinuation of treatment, patients, regardless of reason for treatment discontinuation, will be followed for safety for 30 days after the last dose.<br><br>Survival information will be collected every 3 months until 2 years after the last patient has enrolled in the study regardless of treatment discontinuation reason (except if consent is withdrawn). If the study primary efficacy endpoint is not met, Novartis may decide not to conduct survival follow up for the study. |
| **Population** | The study population consists of approximately 70-90 adult patients with a diagnosis of a solid tumor or hematological malignancy that have been pre-identified as having ALK or ROS1 positive mutations, translocations, rearrangements or amplifications. Patients must have received at least one prior treatment for their recurrent, metastatic and/or locally advanced disease and have no remaining standard therapy options anticipated to result in a durable response. Patients must have progressive and measurable disease (per RECIST 1.1 or appropriate hematological response criteria) and be in need of treatment.<br><br>This is a signal seeking study, attempting to identify additional patient populations who may benefit from treatment with single agent ceritinib. Tumors currently being studied under some key Novartis-sponsored trials will be excluded. This includes ALK+ non-small cell lung cancer (NSCLC). Patients with ROS1 rearranged NSCLC may be included. Additional tumor types may be excluded during the course of the study at the discretion of Novartis.<br><br>Patients must not have symptomatic cardiac disease or impairment of GI function.<br><br>[redacted] |

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| | Enrollment is meant to encompass solid tumors and hematologic malignancies as having ALK or ROS1 positive mutations, translocations, rearrangements or amplifications that may be inhibited by ceritinib who otherwise meet all the inclusion and none of the exclusion criteria. Though common for phase I studies, tissue-agnostic enrollment is unusual for phase II studies, which typically limit enrollment to one or a few well-defined tumor types. We expect that the study will enroll patients whose tumors have already been pre-identified to harbor ALK or ROS1 positive mutations, translocations, rearrangements or amplifications such as B-cell lymphoma, breast cancer, colorectal cancer, melanoma, Anaplastic Large Cell Lymphoma (ALCL) and ovarian cancer (enrollment will not be strictly limited to those particular cancers). Patients with ROS1 rearranged NSCLC may also be included. The total number of patients to be enrolled per tumor type will be based on an adaptive design. The adaptive design will be patient-sparing and allow the early closure of non-responding arms or arms where early success can be declared. |
| **Inclusion criteria** | Patient has a confirmed diagnosis of a solid tumor (except with a primary diagnosis of ALK+ NSCLC) or hematologic malignancy and is in need of treatment because of progression or relapse<br><br>Patient's tumor has been evaluated and pre-identified as having an ALK or ROS1 positive mutation, translocation, rearrangement or amplification. The qualifying alteration must be assessed and reported by a CLIA-certified laboratory<br><br>Patient must have received at least one prior treatment for recurrent, metastatic and /or locally advanced disease and for whom no standard therapy options are anticipated to result in a durable remission<br><br>Patient must have progressive and measurable disease per RECIST 1.1. or other appropriate hematological response criteria<br><br>Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1<br><br>See Section 5.2 for complete Inclusion criteria |
| **Exclusion criteria** | Patient has received prior treatment with ceritinib<br><br>Patient has received chemotherapy or other anticancer therapy ≤ 4 weeks (6 weeks for nitrosourea, antibodies or mitomycin-C) prior to starting study drug<br><br>Patients with a history of pancreatitis or increased amylase or lipase due to pancreatic disease<br><br>Patients with clinically significant uncontrolled heart disease and/or recent cardiac event (within 6 months)<br><br>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)<br><br>Patients with another primary malignancy within 3 years prior to starting study treatment, with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in-situ carcinoma of the uterine cervix<br><br>See Section 5.3 for complete Exclusion criteria |
| **Investigational and reference therapy** | Ceritinib administered orally once daily at a dose of 750mg (5 capsules of 150 mg ceritinib (LDK378)). A complete treatment cycle is defined as 28 days. |

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| **Efficacy assessments** | All screening evaluations must be performed as closely as possible to the beginning of treatment and never more than 28 days prior to starting study drug dose of ceritinib to confirm patient's eligibility.<br><br>During treatment phase, disease assessments must be performed at screening and every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle), until disease progression or end of treatment, whichever occurs first. The frequency of disease assessment may be reduced to every 12 weeks for patients who have at least 4 post-baseline disease assessments and are clinically stable (except MM and AML patients).<br><br>Patients will continue to receive study treatment until disease progression (assessed by investigator per RECIST 1.1 or appropriate hematologic response criteria), unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator).<br><br>Survival information will be collected every 3 months until 2 years after the last patient has enrolled in the study regardless of treatment discontinuation reason (except if consent is withdrawn). If the study primary efficacy endpoint is not met, Novartis may decide not to conduct survival follow up for the study. |
| **Safety assessments** | Adverse events<br><br>Physical examination including vital signs and weight<br><br>Performance status evaluation<br><br>Cardiac monitoring (cardiac enzymes, ECGs, and assessment of LVEF)<br><br>Laboratory evaluations (hematology, biochemistries, pregnancy tests and urinalysis) |
| **Data analysis** | The Full Analysis Set (FAS) will include all patients who have received at least one dose of study drug. FAS will be the primary population for the analysis of efficacy endpoints. |
| **Key words** | Solid tumor malignancy, hematologic malignancy, mutation, translocations, signature, ALK, ceritinib, ROS1, NSCLC, B-cell lymphoma, breast cancer, colorectal cancer, melanoma, ALCL, and ovarian cancer |

# 1 Background

## 1.1 Overview of disease pathogenesis, epidemiology and current treatment

### 1.1.1 Ceritinib target pathway

ALK is a receptor tyrosine kinase of the insulin receptor superfamily that plays a role in neural development and function. ALK gene rearrangements result in aberrant ALK activation, and ALK fusion proteins possess potent oncogenic activity in both *in vitro* and *in vivo* models. This activity can be effectively blocked by small-molecule inhibitors that target ALK.

For further details on clinical and non-clinical experience, refer to the [LDK378 Investigator's Brochure].

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

### 1.2.1 Overview of ceritinib

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

In addition, ceritinib shows potent antitumor activity in crizotinib-resistant animal models (as described below), and the efficacy seen in the 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:

'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 indications:

- 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.

Ceritinib has demonstrated potent antitumor activity in patients with advanced, ALK-rearranged NSCLC (Shaw et al 2014). As reported in Shaw, et al 2014 a total of 130 patients were treated: 59 patients in the dose-escalation phase and 71 in the expansion phase. Eligible patients had a locally advanced or metastatic cancer harboring genetic alterations in ALK. 122 (94%) patients had NSCLC, among the eight patients with advanced cancers other than NSCLC, two had a response to ceritinib: one patient with anaplastic large-cell lymphoma, and one with inflammatory myofibroblastic tumor.

### 1.2.2 Discovery of ROS1 rearrangement and its impact in NSCLC

ROS1 is a receptor tyrosine kinase of the insulin receptor family with constitutive kinase activity. ROS1 rearrangement was initially found in glioblastoma and was shown to have oncogenic potential by Charest et al., using transgenic mouse model. Rikova et al. and Li et al. also reported ROS1 rearrangement in NSCLC and currently at least 13 known ROS1 fusion variants involving 8 fusion partners were identified in ROS1 positive NSCLC. ROS1 rearrangement is found in 1-2% of NSCLC and defines a unique molecular subset of NSCLC. ROS1 rearrangement in NSCLC is characterized by younger age of onset and history of never or light smokers with adenocarcinoma histology. Bergethon et al. screened 1073 NSCLC tumors and identified 18 (1.7%) patients with ROS1 rearrangement by break-apart FISH assay. The median age of the 18 ROS1-rearranged NSCLC patients was 49.8 years (range: 32-79 years), 78% were never-smokers and all of them presented with adenocarcinoma. ROS1 rearrangement is known to be mutually exclusive with other oncogenic mutations such as epidermal growth factor receptor (EGFR) mutation, KRAS mutation or ALK rearrangement.

Preclinical studies have shown that cell lines and tumors harboring ROS1 fusion are sensitive to crizotinib, a dual ALK/MET inhibitor. Furthermore, cells harboring ROS1 fusions did not respond to treatment with EGFR-targeted kinase inhibitors. In accordance with preclinical data, preliminary results of a phase I clinical trial of crizotinib in the ROS1-rearranged NSCLC showed remarkable efficacy of crizotinib with an overall response rate of 57% at 8 weeks of treatment. Altogether, these results define ROS1-rearranged NSCLC as a distinct druggable entity and highlight the importance of identification of ROS1-rearranged patients who will benefit from ROS1-targeted therapy.

#### Rationale for the use of ceritinib in ROS1-driven NSCLC

Ceritinib is an orally highly selective and potent ALK kinase inhibitor. Ceritinib is a potent inhibitor of tumor growth in rodent models of both anaplastic large cell lymphoma (ALCL) and NSCLC. Preclinical studies showed that ceritinib also has nanomolar-range IC50 values in cell lines engineered to express ROS1 rearrangement. ALK and ROS1 kinase domain share approximately 49% amino acid sequence homology, and several ALK inhibitors have been shown to inhibit ROS1. A recent finding with an *in silico* method showed that high number of conserved residues in the ALK and ROS1 kinase domains interacted with an ALK inhibitor, TAE684.

The ongoing phase I study of ceritinib has demonstrated preliminary evidence of antitumor activity in ALK positive NSCLC. Section 1.2.4.1.1 details the efficacy of ceritinib from this study. This available data provides rationale for the clinical activity of ceritinib and is expected to bring benefit to ROS1-rearranged population in a similar aspect.

### 1.2.3 Non-clinical experience

#### 1.2.3.1 Non-clinical 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 the ALK kinase activity. In a kinase panel of 35 additional enzymes, ceritinib demonstrated a high degree of selectivity for ALK inhibition by inhibiting only 2 other kinases (INSR and IGF1R) but with approximately 50-fold less potency than ALK inhibition.

Inhibition of fusion oncogenes NPM-ALK and EML4-ALK in mouse and rat xenograft models resulted in inhibition of tumor growth and tumor regression *in vivo*. Ceritinib was also active in cell lines with ALK amplification or expression of activating point mutations. Ceritinib is highly active in mouse and rat xenograft models of lung cancer and ALCL that carry an ALK rearrangement. In murine xenograft models of H2228 NSCLC and Karpas299 ALCL cells, ceritinib dosed at 25mg/kg daily, a dose below the maximum tolerated dose (MTD) in clinical studies, resulted in complete regression of established tumors.

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

#### 1.2.3.2 Non-clinical pharmacokinetics and metabolism

In general, ceritinib was moderately absorbed in rats (37%) and monkeys (>40%). Oral bioavailability was complete in fed dogs, suggesting the possible existence of a positive food effect. The formulation used in these bioavailability determinations was a 0.5% methylcellulose suspension except for in the mouse where a solution formulation was used. Ceritinib is highly bound to plasma protein (>94%) in all species. Following oral administration of [$^{14}$C] ceritinib to LEH male rats, radioactivity was widely distributed. The highest tissue exposures were found in intestine wall, uveal tract, pituitary gland, bile, adrenal cortex, harderian gland, liver, spleen, lymph node, lung, kidney, thyroid, bone marrow, adrenal medulla and pancreas (25 to 710-fold higher exposure relative to blood). Although the brain to blood concentration ratio of drug-related radioactivity was low compared to these other tissues brain-to-blood exposure (AUCinf) ratio of approximately 15%, it was higher than the 3% background associated with brain vasculature at all monitored time points. This indicates that drug-related radioactivity crossed the blood-brain barrier. Unchanged ceritinib was the major component in feces and bile of intact and bile duct-cannulated rats. In the rat, ceritinib underwent oxidation leading to the formation of four oxygenated metabolites (designated as M23.6, M30.6, M35.8, and M33.4). In addition, ceritinib underwent sulfation leading to M36.8 and oxidation followed by sulfation resulting in the presence of M29.5. Ceritinib also underwent glucuronidation leading to M26.8 and M27.6. The major metabolite in feces was designated M33.4 (oxygenation) accounting for approximately 7% of the dose. All other metabolites in feces and bile were minor (<5% of the dose). In rats dosed with [$^{14}$C] ceritinib, ceritinib -derived radioactivity was excreted predominantly via the fecal route

(>99%), and renal excretion was a minor pathway for excretion (<1%). Fecal excretion was the result of biliary excretion (69%) and gastrointestinal (GI) secretion (31%). Since parent drug was the major component in bile and feces after intravenous administration, enterohepatic circulation may occur.

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

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

#### 1.2.3.3 Safety pharmacology and toxicology

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

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

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

Preclinical studies including an *in vitro* 3T3 NRU assay (refer to [Investigators Brochure]), indicated a low risk of phototoxicity with the use of ceritinib. In addition, a preliminary

analysis from an *in vivo* ultraviolet local lymph node assay (UV LLNA) demonstrated no phototoxic potential with ceritinib.

### 1.2.4 Clinical experience

#### 1.2.4.1 Clinical safety and tolerability

Ceritinib is associated with a manageable safety profile (Table 1-1). For the 255 patients treated at the recommended dose of 750 mg in the ongoing study [CLDK378X2101], the median duration of exposure as of the 31-Oct-2013 cut-off date was 26.9 weeks (range 0.4 to 82.3 weeks). The most common adverse events 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 10%) and associated grade 3-4 adverse events, regardless of study drug relationship, by preferred term in patients treated in the 750 mg dose group (Data cut-off date: 31-Oct-2013)**

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

| | Ceritinib 750 mg N=255 | |
|---|---|---|
| | All Grades | Grade 3/4 |
| Preferred term | n (%) | n (%) |
| Pyrexia | 38 (14.9) | 0 |
| Rash | 32 (12.5) | 0 |
| Insomnia | 31 (12.2) | 0 |
| Dyspepsia | 26 (10.2) | 1 (0.4) |
| Hypokalemia | 26 (10.2) | 11 (4.3) |
| Dizziness | 26 (10.2) | 0 |

Dose reductions due to adverse events (AEs) occurred in 584% of patients treated with ceritinib at the 750 mg dose; 38.8% of patients had only 1 dose reduction. The most frequent AEs requiring dose adjustments or interruptions reported in >5% of the patients were: ALT increased, nausea, AST increased, vomiting, diarrhea, fatigue, and abdominal pain. Adverse events leading to study drug discontinuations occurred in 10.2% of patients treated with ceritinib at the 750 mg dose. The most frequent AEs leading to study drug discontinuations were decreased appetite, pneumonia, ALP increased, pneumonitis, and respiratory failure.

Serious adverse events (SAEs) reported in 2% or more of the 255 patients treated at the recommended dose of 750 mg were convulsion, pneumonia, interstitial lung disease (ILD)/pneumonitis, dyspnea, hyperglycemia, and nausea. Fatal adverse reactions occurred in 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 to be monitored for ceritinib have also been identified and include hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia, gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations). For additional details, refer to the [Investigator's Brochure].

#### 1.2.4.1.1 Clinical efficacy

As of 31-Oct-2013, data from the ongoing study [CLDK378X2101] demonstrated a high rate of rapid and durable responses with ceritinib in 246 ALK-positive NSCLC patients treated in the 750 mg dose group (RD). In these patients the overall response rate (ORR) was 58.5% (95% CI: 52.1, 64.8) based on investigator assessment (Table 1-2). Among the 144 ALK-positive NSCLC patients with a confirmed complete response (CR) or partial response (PR) based on investigator assessment, 86.1% of those patients achieved a response within 12 weeks, with a median time to response of 6.1 weeks (range: 3.0 to 24.1). The estimated median duration of response (DOR) based on investigator assessment was long at 9.69 months (95% CI: 7.00, 11.40). Based on investigator assessment, the median PFS was 8.21 months (95% CI: 6.70, 10.12) with 53.3% of the patients censored at the end of the study. Importantly, ceritinib showed this level of high anti-cancer activity regardless of prior ALK inhibitor status (i.e., whether or not the patient received previous treatment with an ALK inhibitor). A high ORR of 54.6% and 66.3% was observed in patients treated with a prior ALK inhibitor and in ALK inhibitor naïve patients, respectively, by investigator assessment (Table 1-2). Rapid responses were observed in patients regardless of prior ALK inhibitor

status, 6.1 weeks (range: 4.6 to 24.1) in patients treated with a prior ALK inhibitor and 6.1 weeks (range: 3.0 to 24.1) in 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 and, the median DOR in the latter group was not reached in ALK inhibitor naïve patients, however the 12-month DOR rate was 65.2% (95% CI: 46.4, 78.8). The estimated median PFS was 6.90 months (95% CI: 5.39, 8.41) in patients treated with a prior ALK inhibitor, while the median PFS was not reached in ALK inhibitor naïve patients (95% CI: 8.31, NE) Finally, ceritinib demonstrated activity in patients with brain metastasis at baseline. Among the 98 patients with brain metastasis who had received prior ALK-inhibitor treatment, the ORR was 50% (95% CI: 39.7, 60.3), DOR was 6.9 months (95% CI: 4.8, 8.5), and PFS was 6.7 months (95% CI: 4.9, 8.4). For additional details, refer to [Investigator's Brochure].

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

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

This table presents data for all patients with ALK-positive NSCLC in the 750 mg treatment dose group, **FAS-NSCLC 750 mg group**
Best overall response is based on 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

### 1.2.4.1.2 Clinical pharmacokinetics

In adult patients with tumors characterized by genetic abnormalities in ALK study [CLDK378X2101] and in healthy volunteers study [CLDK378A2101], study [CLDK378A2104] and study [CLDK378A2106], single-dose pharmacokinetics of ceritinib in humans has the following features: (1) ceritinib was slowly absorbed, with median peak plasma concentration occurring at approximately 4 to 6 h in patients, and approximately 6 to 8 h in healthy subjects. Following Cmax, ceritinib concentrations declined in a mono-exponential manner. The geometric mean apparent terminal half-life ranged from 31 to 41 h across the 400 to 750 mg dose groups in patients and 36 to 48 h across the 450 to 750 mg dose groups in healthy subjects. (2) Cmax and AUClast increased dose-proportionally following single oral administration of ceritinib across the 50 to 750 mg dose groups in patients. (3) moderate to high variability in ceritinib PK parameters has been observed in both healthy

subjects and patients. Following single oral doses of 450 to 750 mg in healthy subjects when ceritinib was given alone, the inter-subject variability (geometric mean coefficient of variation; CV% range) was 42-74% and 35-72% for AUClast and Cmax, respectively. The corresponding values in patients were 93% and 87% following single oral doses of 50 to 750 mg based on a model developed for dose proportionality analysis.

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

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

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

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

To further clarify if low fat content has an impact on the extent of ceritinib absorption, a food effect assessment with a very low-fat light snack (containing approximately 100-300 calories

and 1.5 grams of fat) was also explored in an ongoing relative bioavailability study conducted in healthy subjects [Study CLDK378A2108]. PK data from the light snack cohort showed that when a single 750 mg oral dose of ceritinib was administered with a light snack, the Cmax and AUCinf increased by 45% and 54% respectively, compared to the fasted condition. This magnitude of increase is similar to that caused by a low-fat meal as described in Study CLDK378A2101, suggesting that even a very low-fat meal could lead to a clinically meaningful ceritinib exposure increase.

### 1.3 Risk and Benefits

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

Based on the experience from the ongoing single-agent ceritinib studies, the efficacy and safety profile of ceritinib was considered to be acceptable for continued clinical development. Data from these studies indicate that ceritinib provides a high rate of durable responses in patients with ALK-rearranged NSCLC, both in patients who have been previously treated with crizotinib and in those who are crizotinib-naïve. There may be unforeseen risks with ceritinib which could be serious.

## 2 Rationale

### 2.1 Study rationale and purpose

Genomic profiling is becoming more accessible to patients and their physicians. As such, more patients have been identified with potentially actionable genomic alterations or pathway-activations but do not have access to targeted drug treatment. This is a signal seeking study to match patients with ALK or ROS1 positive mutations, translocations, rearrangements or amplifications to treatment with the ALK kinase inhibitor ceritinib. Pre-identification of ALK or ROS1 positive mutation, translocation, rearrangement or amplification status will be performed locally at a CLIA certified laboratory prior to participation on the trial.

The purpose of this signal seeking study is to determine whether treatment with ceritinib demonstrates sufficient efficacy in select pathway-activated solid tumors and/or hematologic malignancies to warrant further study. Patients with ALK+ NSCLC will be excluded from this exploratory study because this indication is currently being studied under key Novartis-sponsored ceritinib trials. Patients with ROS1 rearranged NSCLC may be included. Additional tumor types may be excluded during the course of the study at the discretion of Novartis.

Details of the study design are provided in Section 4.

Additionally, increased understanding of the genomic changes in tumors allows the selection of patients more likely to benefit from treatment. In most cases patients who respond well initially to treatment soon develop resistance to the new treatments; also, many patients have disease that does not respond. The biological complexity of cancers and lack of knowledge of the mechanisms responsible for resistance in patients pose challenges, therefore a successful development of treatments that provide sustained disease control or cure requires improving the understanding of the mechanisms responsible for drug resistance. Therefore, in patients

with a best response of SD or better, an optional tumor sample at the time of disease progression could be obtained for genomic analysis.

[redacted]

## 2.2 Rationale for the study design

This is a phase II, open label study to determine the efficacy and safety of treatment with ceritinib in patients with a diagnosis of solid tumors or hematological malignancies that have been pre-identified (prior to study consent) to have ALK or ROS1 positive mutations, translocations, rearrangements or amplifications and whose disease has progressed on or after standard treatment.

## 2.3 Rationale for dose and regimen selection

The recommended ceritinib phase II dose is 750 mg/day which corresponds to the single agent recommended phase two dose (RP2D). The selection of the starting dose follows the ICH S9 guidelines for choosing a starting a dose for a first-in-human trial conducted in patients with cancer, and is shown in Table 6-2. It will be dosed on a flat scale and not adjusted by weight or body surface area.

# 3 Objectives and endpoints

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

**Table 3-1 Objectives and related endpoints**

| Objective | Endpoint | Analysis |
|---|---|---|
| **Primary:**<br>● To assess clinical benefit associated with ceritinib treatment based on local investigator assessment.<br>● For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR or PR or SD. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices. | ● Clinical benefit rate (e.g. defined as CR or PR or SD ≥ 16 weeks for solid tumors). For hematologic tumors, other appropriate hematological response criteria will apply and are included in the appendices. | Refer to Section 10.4 |
| **Key secondary:**<br>● To assess Overall Response (OR) of Partial Response (PR) or greater based on local investigator assessment.<br>● For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices. | ● Overall response rate (PR or greater) | Refer to Section 10.5.1 |
| **Other secondary:** | | |
| ● To assess Progression-Free Survival (PFS) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria | ● Time from the date of first dose to the date of first documented disease progression or relapse or death due to any cause | Refer to Section 10.5.2 |
| ● To assess Overall Survival (OS) | ● Time from the date of first dose to the date of death due to any cause | Refer to Section 10.5.2 |
| ● To assess Duration of Response (DOR) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria | ● Time from the first documented response to the date first documented disease progression or relapse or death due to any cause | Refer to Section 10.5.2 |
| ● To assess safety and tolerability | ● Incidence of AEs, SAEs, changes from baseline in vital signs, laboratory test results(hematology, biochemistry), ECG, and cardiac imaging will be assessed by the Common Terminology Criteria for Adverse Events (CTCAE), v4.03 | Refer to Section 10.5.3 |

[redacted]

# 4 Study design

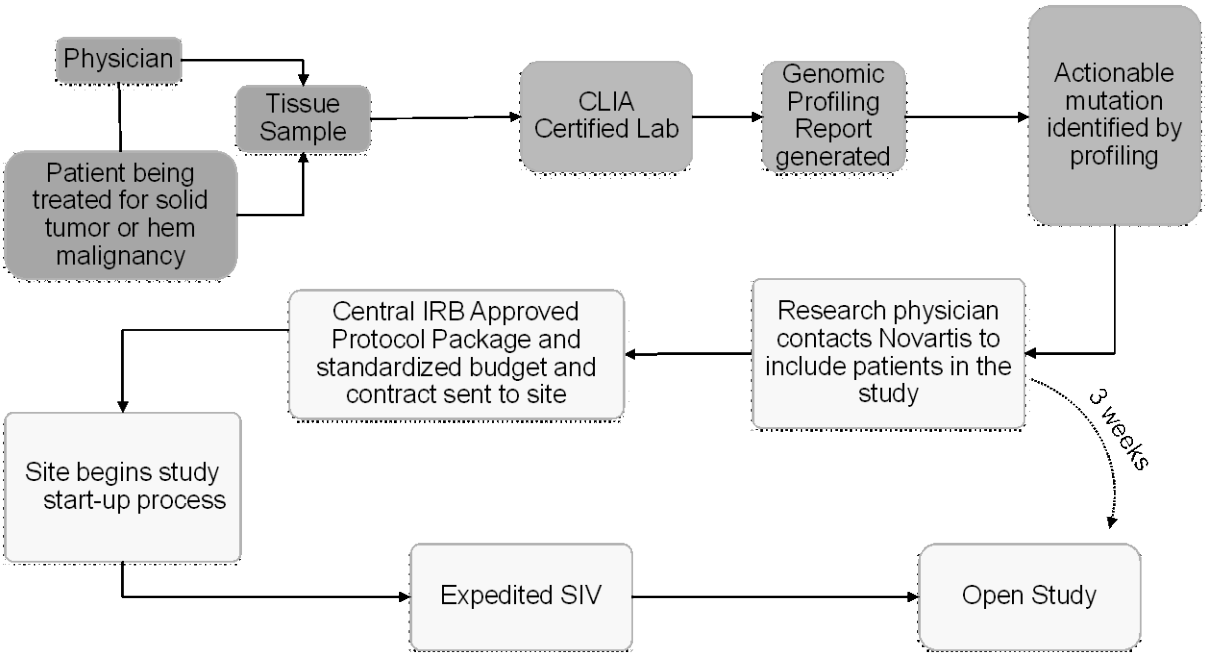
## 4.1 Description of study design

This is a phase II, open label study to determine the efficacy and safety of treatment with ceritinib in patients with a diagnosis of solid tumors or hematological malignancies that have been pre-identified (prior to study consent) to have ALK or ROS1 positive mutations, translocations, rearrangements or amplifications and whose disease has progressed on or after standard treatment.

This study is intended for patients who have already had genomic profiling of their tumors in a CLIA certified laboratory and have already been pre-identified to have a tumor with an ALK or ROS1 positive mutation, translocation, rearrangement or amplification. Eligibility is based on ALK or ROS1 positive mutation, translocation, rearrangement or amplification status as assessed in the local, CLIA certified laboratory. The results of this testing must be known prior to signing the ICF and before formal screening begins. Once the patient has been identified, treating physicians who are qualified investigators may contact Novartis to consider enrollment in this study. For the purpose of this study, genomic profiling is not considered part of screening. Informed consent must be signed before any screening activities take place. Once eligibility (screening criteria met) has been confirmed by Novartis, the patient will initiate therapy with ceritinib single-agent. The patient may not receive any additional anti-cancer therapy during treatment with ceritinib.

A schematic representation of the study start-up design is shown in Figure 4-1.

**Figure 4-1 Study Start-up Design**



### 4.1.1 Treatment phase

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

Disease assessments (per RECIST 1.1 or appropriate hematological response criteria) will be performed every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle), until disease progression or end of treatment, whichever occurs first. The frequency of disease assessment may be reduced to every 12 weeks for patients who have at least four post-baseline disease assessments and are clinically stable (except MM and AML patients). Scans will be assessed locally by the investigator.

### 4.1.2 Follow-up phase

After discontinuation of treatment, patients, regardless of reason for treatment discontinuation, will be followed for safety for 30 days after the last dose.

Survival information will be collected every 3 months until 2 years after the last patient has enrolled in the study regardless of treatment discontinuation reason (except if consent is withdrawn). If the study primary efficacy endpoint is not met, Novartis may decide not to conduct survival follow up for the study. For details on required assessments, please refer to Table 7-1.

For patients with a best response of SD or better who discontinue study treatment due to disease progression, an optional tumor sample should be obtained for genomic analysis. This tumor sample must be obtained within 28 days of stopping the study treatment and no more than 14 days after starting another treatment for their cancer (at a time most convenient for the patient); exceptions may be made after discussion with the sponsor. [redacted]

## 4.2 Definition of end of the study

End of study is defined as the time when the last patient completes survival follow-up, has expired, is lost to follow up or withdraws consent, or when the study is terminated early.

The analysis of study data will be based on all patients' data up to the time when all patients have had the opportunity to complete at least 4 cycles (or 16 weeks) of treatment or discontinued the study. This will be the cut-off point for the primary clinical study report (CSR). Additional data for patients continuing to receive study treatment past the data cutoff date for the primary CSR will be reported once all patients have discontinued treatment or been lost to follow-up. It will be reported in an addendum to the CSR, as appropriate.

At the time of CSR data cut-off, if patients are ongoing after 16 weeks on treatment and benefitting, they will continue to receive treatment in the current study until enrollment into a separate protocol.

### 4.3 Early study termination

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

## 5 Population

### 5.1 Patient population

The study population will consist of 70-90 adult patients with a diagnosis of a solid tumor or hematological malignancy that has been pre-identified as having ALK or ROS1 positive mutations, translocations, rearrangements or amplifications. Patients must have received at least one prior treatment for their recurrent, metastatic and/or locally advanced disease and have no remaining standard therapy options anticipated to result in a durable response. Patients must have progressive and measurable disease (per RECIST 1.1 or other appropriate hematological response assessment criteria) and be in need of treatment. This is a signal seeking study, attempting to identify additional patient populations who may benefit from treatment with single agent ceritinib. Tumors currently being studied under some key Novartis-sponsored trials will be excluded. This includes ALK+ NSCLC. Patients with ROS1 rearranged NSCLC may be included. Additional tumor types may be excluded during the course of the study at the discretion of Novartis.

Patients must not have symptomatic cardiac disease, or impairment of gastrointestinal (GI) function. [redacted]

Enrollment is meant to encompass solid tumors and hematologic malignancies as having ALK or ROS1 positive mutations, translocations, rearrangements or amplifications that may be inhibited by ceritinib who otherwise meet the all of the inclusion and none of the exclusion criteria. Though common for phase I studies, tissue-agnostic enrollment is unusual for phase II studies, which typically limit enrollment to one or a few well-defined tumors types. We expect that the study will enroll patients whose tumors have already been pre-identified to harbor ALK or ROS1 positive mutations, translocations, rearrangements or amplifications such as B-cell lymphoma, breast cancer, colorectal cancer, melanoma, ALCL and ovarian cancer (enrollment will not be strictly limited to those particular cancers). Patients with ROS1 rearranged NSCLC may also be included. The total number of patients to be enrolled per tumor type will be based on an adaptive design. The adaptive design will be patient-sparing and allow the early closure of non-responding arms or arms where early success can be declared.

## 5.2 Inclusion criteria

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

1. Patient has provided a signed study Informed Consent Form prior to any screening procedure
2. Patient is ≥ 18 years of age on the day of consenting to the study
3. Patient has a confirmed diagnosis of a solid tumor (except ALK+ NSCLC) or hematological malignancy and is in need of treatment because of radiologic progression or relapse. Patients with ROS1 rearranged NSCLC may be included. Additional tumor types may be excluded during the course of the study at the discretion of Novartis.
4. Patient is in need of treatment because of progression or relapse defined as:
   - radiological progression for solid tumor and lymphoma
   - for hematologic malignancies, measureable progression or relapse by appropriate criteria (see appendices)
5. Patient must have been pre-identified as having a tumor with an ALK or ROS1 positive mutation, translocation, rearrangement or amplification. The qualifying alteration must be assessed and reported by a CLIA-certified laboratory. ALK positivity as assessed by IHC or FISH are allowed. [redacted]. The sample must be submitted prior to first study dose unless agreed upon between Novartis and the investigator. See Section 7.2.4.2.1.
6. Patient must have received at least one prior treatment for recurrent, metastatic and/or locally advanced disease and for whom no standard therapy options are anticipated to result in a durable remission
7. **Diffuse large B cell lymphoma only**: Patient has received or is ineligible for autologous or allogeneic stem cell transplant. This does not apply to patients with Mantle cell lymphoma or follicular lymphoma
8. Patients must have measurable disease as per appropriate guidelines:
   a. **Solid Tumors:** by RECIST 1.1 (Appendix A)
   b. **Lymphoma**: Patient has at least one measurable nodal lesion (≥2 cm) according to Cheson criteria (Cheson 2007). In case where the patient has no measurable nodal lesions ≥ 2 cm in the long axis at screening, then the patient must have at least one measurable extra-nodal lesion (Appendix B)
   c. **Symptomatic Multiple Myeloma:** by International Myeloma Working Group (IMWG)
      - Serum M-component of ≥1 gm/dL
      - Urine M-component of ≥200 mg/24 h
      - Patients with plasmacytoma must have a definite increase in the size; a definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
   d. **Leukemia only:** Relapsed/refractory leukemia for which no standard therapy options are anticipated to result in a durable remission:

- Acute myelogenous leukemia (AML) by World Health Organization (WHO) classification or acute lymphoblastic leukemia (ALL) relapsed or refractory to standard chemotherapy; unsuitable for standard chemotherapy or unwilling to undergo standard chemotherapy. Philadelphia chromosome (Ph) positive ALL eligible if failed prior tyrosine-kinase inhibitor therapy.
- Age > 60 years with AML not candidates for or have refused standard chemotherapy, excluding patients with acute promyelocytic leukemia (APL) or with favorable cytogenetic abnormalities [inv16, t(8;21)]
- For patients with Chronic Myeloid Leukemia (CML) only accelerated and blast phase CML will be allowed

9. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (Appendix M)
10. Patient has a life expectancy of at least 16 weeks
11. Patients must have adequate bone marrow as described below:
    a. Absolute Neutrophil Count (ANC) ≥ 1.5 x $10^9$/L (not applicable for leukemia patients)
    b. Platelets (PLT) ≥ 75 x $10^9$/L (no platelet transfusion within past 14 days) (not applicable for leukemia patients)
    c. Hemoglobin (Hgb) ≥ 8 g/dl (not applicable for leukemia patients)
12. Patient must meet the following laboratory values at the screening visit:
    - International Normalized Ratio (INR) ≤ 1.5
    - Serum amylase ≤2 x ULN
    - Serum lipase ≤ ULN
    - Alkaline phosphatase (ALP) ≤ 5.0 x ULN
    - Fasting plasma glucose ≤ 175 mg/dL (≤ 9.8 mmol/L)
13. All patients must have adequate organ function defined as described below:
    a. Potassium, calcium (corrected for serum albumin), phosphorus and magnesium within normal limits (WNL). Supplementation is allowed to meet eligibility requirements
    b. Serum creatinine < 1.5 mg/dl and/or calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 30 mL/min
    c. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 3.0 x upper limit of normal range (ULN) or ≤ 5 x ULN if liver metastases are present
    d. Total serum bilirubin within normal range or ≤ 1.5 x ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin ≤ 3 x ULN or direct bilirubin ≤ 1.5 x ULN
14. For Leukemia patients, peripheral blast counts < 50,000 blasts/$mm^3$

## 5.3 Exclusion criteria

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

1. Patients who have received prior treatment with ceritinib
2. Patients with a known hypersensitivity to ceritinib or to its excipients (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate)

3. Patients with history of carcinomatous meningitis
4. Patients with symptomatic CNS metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms
5. Patients with diarrhea CTCAE ≥ grade 2
6. Patients with neuropathy CTCAE ≥ grade 2
7. Patients with a history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease
8. Patients with external biliary drains
9. Patients with a history of pulmonary embolism (PE), or untreated deep venous thrombosis (DVT) ≤ 6 months prior to starting study drug

   Note: Patients with recent DVT who have been treated with therapeutic anti-coagulant agents for at least 6 weeks are eligible.
10. 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)
11. 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
12. 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 may interfere with the interpretation of study results
13. Patients with clinical evidence of active CNS leukemia
14. Patients who have received Allogeneic stem cell transplant and/or have active graft-versus-host disease (GVHD)
15. Patient has received Autologous stem cell transplant within last 4 weeks
16. Impairment of GI function or GI disease that may significantly alter the absorption of ceritinib (e.g. severe ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)

17. Any other condition that would, in the investigator's judgment, contraindicate patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g. infection/inflammation, intestinal obstruction, social/psychological complications
18. Patients who have been treated with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated at least 2 weeks prior to enrollment, may be continued. Restriction is not applicable for patients with leukemia
19. Patient has received chemotherapy or anticancer therapy ≤ 4 weeks (6 weeks for nitrosourea, monoclonal antibodies or mitomycin-C) prior to starting study drug or who have not recovered to ≤ grade 2 from side effects of such therapy (except for alopecia and neuropathy). Patients with leukemia may receive therapy with hydroxyurea and/or steroids for the purpose of cytoreduction but must discontinue use prior to first dose of study drug.
20. Patients who have received the last administration of an anticancer targeted small molecule therapy (e.g. sunitinib, pazopanib, everolimus) ≤ 2 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy
21. Patients not able to discontinue their current anti-cancer therapy prior to first dose of study drug
22. 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 starting study treatment is allowed.
23. Patients who have undergone major surgery (e.g., intra-thoracic, intra-abdominal, intra-pelvic) ≤ 4weeks prior to starting study treatment or who have not recovered from side effects of such surgery. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can receive study treatment ≥ 1 week after these procedures
24. Patients with another primary malignancy within 3 years prior to starting study treatment, with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in-situ carcinoma of the uterine cervix.
25. Patients 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:
    a. Strong inhibitors or strong inducers of CYP3A4/5 (Appendix P).
    b. Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5 and/or CYP2C9 (Appendix P).
    c. Medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes (Appendix P)
26. Patients who are currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants
27. Patients receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms (non-CNS), dose

must have been stabilized (or decreasing) for at least 5 days before first dose of study treatment

28. Patients receiving treatment with any enzyme-inducing anticonvulsant (Appendix P) 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.
29. Cirrhosis of the liver or known hepatitis B or C infection that is either acute or is considered chronic because the virus did not become undetectable:
    a. Hepatitis C Virus (HCV) infection: acute or chronic infection as depicted by a positive HCV RNA testing (note: in a patient with known anti-HCV but with a negative test for HCV RNA, re-testing for HCV RNA 4-6 months later is requested to confirm the resolution of HCV infection)
    b. Hepatitis B Virus (HBV) infection: acute infection (HBsAg+ with or without HBeAg+ or detectable serum HBV DNA), HBV carriers as evidence by ongoing presence of HBsAg and detectable serum HBV DNA levels
30. Patients who have received investigational agents within $\leq 5t_{1/2}$ of the agent (or $\leq 4$ weeks when half-life is unknown) prior to starting study drug
31. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)
32. Patient has a history of non-compliance to medical regimen
33. Pregnant or nursing (lactating) women, confirmed by a positive hCG laboratory test
34. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception (defined below). Highly effective contraception must be used by both sexes (female patients and their male partners) during dosing and for 3 months after the last dose of study 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.

    Reliable double-barrier contraception method should be used and maintained throughout the study and for 3 months after study treatment discontinuation.

Women of child-bearing potential (sexually mature) who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 14 days prior to starting study drug.

Post-menopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks prior to entry in the study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment, then she will be considered not of child bearing potential.

35. Fertile males not willing to use contraception. Fertile males must use condom with spermicide. Highly effective contraception, as defined above, must be used by both sexes (male patients and their female partners) during study treatment and for 3 months after the last dose of study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

# 6 Treatment

## 6.1 Study treatment

The investigational or study drug to be used in the course of this trial is ceritinib.

Novartis Drug Supply Management or its designee will provide ceritinib as 150 mg hard gelatin capsules as individual patient supply, packaged in bottles or blisters. Ceritinib will be dosed on a flat scale and not be adjusted to body weight or body surface area.

### 6.1.1 Dosing regimen

Ceritinib will be dosed on a flat scale of 750 mg (e.g., 5 x 150 mg capsules) once daily on a continuous dosing cycle. A complete treatment cycle is defined as 28 days. There will be no breaks between dosing cycles (refer to Table 6-1).

The patient must continue to meet all eligibility criteria on C1D1, as they did during the screening period. Refer to Section 7.1 for more details.

**Table 6-1 Dose and treatment schedule**

| Study treatments | Pharmaceutical form and route of administration | Dose | Frequency and/or Regimen |
|---|---|---|---|
| ceritinib | Capsule for oral use | 750 mg/day (5 x 150 mg capsule) | Daily |
| Different formulations and strengths of ceritinib can be used once these are approved | | | |

#### 6.1.1.1 Ceritinib administration

The following general guidelines should be followed for administration.

- Patients should take ceritinib once daily at approximately the same time each day, in the morning, afternoon, or evening.
- ECG monitoring: Patients should take ceritinib in the morning to accommodate clinic visits when ECG evaluations are conducted.
- Patients should take ceritinib 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 ceritinib should be taken with a glass of water and consumed over as short a time as possible (i.e., not slower than 1 capsule every 2 minutes). Patients should be instructed to swallow whole capsules and not to chew or open them.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

Patients 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 usual daily dosing. That day's dose (or partial remaining dose) should be omitted, and the patient should continue treatment with the next scheduled dose on the following day.

- All dosages prescribed and dispensed to the patient, and all dose changes during the study, must be recorded on the Dosage Administration Record eCRF. Patients must be advised to bring their unused ceritinib capsules/tablets to the investigative site at each visit.

### 6.1.2 Guidelines for continuation of treatment

Patients will be treated until disease progression (as assessed by investigator per RECIST 1.1 or appropriate hematologic response criteria) or unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator). Guidance for continuation of study treatment in case of toxicity (e.g. dose delay and/or modification) is provided in Section 6.3.

### 6.1.3 Treatment duration

Patients may continue treatment with the study drug until the patient experiences unacceptable toxicity that precludes further treatment, disease progression as assessed by the investigator (per RECIST 1.1 or appropriate hematological response assessment criteria), death and/or treatment is discontinued due to any other reason. The reason EOT will be recorded in the corresponding eCRF.

## 6.2 Dose escalation guidelines

Not applicable.

## 6.3 Dose modifications

### 6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule despite maximal medical support (e.g. loperamide, ondasetron), dose adjustments are permitted in order to

allow the patient to continue the study treatment. Any changes in ceritinib administration must be recorded on the Dosage Administration Record eCRF.

Ceritinib dose modification guidelines are described in Section 6.3.2. Any planned variance from these guidelines in the view of the patient safety must be previously 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 for adverse events (NCI-CTCAE version 4.03). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycle.

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

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

### 6.3.2 Permitted study treatment adjustments for ceritinib

For patients who are unable to tolerate the protocol-specified dosing schedule, dose reductions or interruptions are permitted to manage drug-related toxicities.

- When dose reduction is necessary, the dose of ceritinib may be reduced to 600 mg, QD.
- If an additional dose reduction is required, ceritinib may be reduced to 450 mg, QD.
- If an additional dose reduction is required, ceritinib may be reduced to 300 mg, QD.
- Once the ceritinib dose is reduced it cannot be re-escalated.
- All dose reductions should be based on the worst preceding toxicity.
- Patients are allowed only 3 dose reductions (to 600 mg and 450 mg, and 300 mg) as specified in (Table 6-2).

**Table 6-2 Ceritinib dose modifications**

| Ceritinib **Dose Level** | Ceritinib **Dose*** |
|---|---|
| Starting dose level (0) | 750 mg po QD |
| Dose level – 1 | 600 mg po QD |
| Dose level – 2 | 450 mg po QD |
| Dose level – 3 | 300 mg po QD** |

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

### 6.3.3 Criteria for interruption and re-initiation of ceritinib treatment

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

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

If treatment with ceritinib is withheld for more than 21 consecutive days (counting from the first day when a dose was missed) due to treatment-related toxicity, then ceritinib should be permanently discontinued except in cases where the investigator believes the patient continues to derive clinical benefit. In such cases, treatment with ceritinib may be resumed at a lower dose.

Patients whose treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event. Detailed guidelines for follow-up of study drug related AEs or abnormal laboratory values must be followed as described in Section 6.3.4.

All patients will be followed for safety until 30 days after the last dose of ceritinib. Patients ongoing at the time of data cutoff for the CSR for this study may continue to receive treatment in the current study until:

- All patients have died or discontinued from the study
- Another clinical study becomes available that can continue to provide ceritinib in this patient population and all patients ongoing are eligible to be transferred to that clinical study
- At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to patients who in the opinion of the Investigator are still deriving clinical benefit.

The final analysis will occur at the end of the study. All available data from all patients up to this cut-off date will be analyzed and summarized in a final CSR.

**Table 6-3 Ceritinib related toxicity management guidelines**

| Worst toxicity (CTCAE 4.03 Grade)* | Dose Modifications for ceritinib |
|---|---|
| **HEMATOLOGICAL** | |
| **Neutropenia (ANC)** | |
| Grade 1 (ANC < LLN - 1.5 x $10^9$/L)<br>Grade 2 (ANC <1.5 and ≥1.0 x $10^9$/L)<br>Grade 3 (ANC <1.0 and ≥0.5 x $10^9$/L) | Maintain dose level |
| Grade 4 (ANC <0.5 x $10^9$/L) | Omit dose until resolved to ≤ Grade 2, then:<br>If resolved in ≤7 days, then maintain dose level<br>If resolved in >7 days, then ↓ 1 dose level |
| Febrile neutropenia<br>(ANC <1.0 x $10^9$/L, with a **single** temperature of ≥38.3 °C or a sustained temperature of ≥38 °C for more than one hour ) | Omit dose until clinically resolved and neutropenia ≤ Grade 2, then ↓ 1 dose level |

| **Worst toxicity (CTCAE 4.03 Grade)*** | **Dose Modifications for ceritinib** |
|---|---|
| **Thrombocytopenia** | |
| Grade 1 (PLT < LLN - 75 x $10^9$/L)<br>Grade 2 (PLT <75 and ≥50 x $10^9$/L) | Maintain dose level |
| Grade 3 (PLT <50 and ≥25 x $10^9$/L) | Omit dose until resolved to ≤ Grade 2, then:<br>If resolved in ≤7 days, then maintain dose level<br>If resolved in >7 days, then ↓ 1 dose level |
| Grade 4 (PLT <25 x $10^9$/L) | Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level |
| **HEPATIC** | |
| **Alkaline phosphatase and/or Gamma-glutamyl transpeptidase (GGT)** | |
| Isolated elevations of any grade | Maintain dose level |
| **Total Bilirubin**** <br>(for patients with Gilbert Syndrome these dose modifications apply to changes in direct [conjugated] bilirubin only) | |
| Grade 1 (> ULN and ≤1.5 x ULN) | Maintain dose level with liver function test (LFTs)*** monitored as per protocol |
| Grade 2 (>1.5 and ≤3.0 x ULN) with AST or ALT ≤3.0 x ULN | Omit dose until resolved to ≤ Grade 1, then:<br>If resolved in ≤7 days, then maintain dose level<br>If resolved in >7 days, then ↓ 1 dose level |
| Grade 3 (>3.0 and ≤10.0 x ULN) with AST or ALT ≤3.0 x ULN | Omit dose until resolved to ≤ Grade 1, then:<br>If resolved in ≤7 days, ↓ 1 dose level<br>If resolved in >7 days discontinue patient from ceritinib |
| Grade 4 (>10.0 x ULN) | Permanently discontinue patient from ceritinib |
| **AST or ALT** | |
| Grade 1 (> ULN and ≤3.0 x ULN) | Maintain dose level with LFTs*** monitored per protocol |
| Grade 2 (>3.0 and ≤5.0 x ULN) without total bilirubin elevation to >2.0 x ULN | Maintain dose level with LFTs*** monitored per protocol |
| Grade 3 (>5.0 and ≤20.0 x ULN) without total bilirubin elevation to >2.0 x ULN | Omit dose until resolved to ≤ Grade 1 (or to baseline), then ↓ 1 dose level |
| Grade 4 (>20.0 x ULN) without total bilirubin elevation to >2.0 x ULN | Omit dose until resolved to ≤ Grade 1 (or to baseline), then ↓ 1 dose level |
| **AST or ALT and concurrent Total bilirubin** | |
| AST or ALT >3.0 x ULN and total bilirubin >2.0 x ULN in the absence of cholestasis or hemolysis | Permanently discontinue patient from ceritinib (Refer to Section 6.3.4.2 for additional follow-up) |
| **PANCREATIC** | |
| **Amylase and/or lipase elevations (in the absence of clinical symptoms)** | |
| Grade 1 (> ULN and ≤1.5 x ULN) | Maintain dose level |
| Grade 2 (>1.5 - 2.0 x ULN) | Maintain dose level |
| Grade ≥3 (> 2.0 x ULN) | Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level |
| Note: Withhold ceritinib for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology. | |
| **RENAL** | |
| **Serum creatinine** | |
| Grade 1 (>1 and ≤1.5 x baseline; > ULN and ≤1.5 x ULN) | Maintain dose level |
| Grade 2 (>1.5 and ≤3.0 x baseline; >1.5 and ≤3.0 x ULN) | Omit dose until resolved to ≤ Grade 1, then:<br>If resolved in ≤7 days, then maintain dose level<br>If resolved in >7 days, then ↓ 1 dose level |
| Grade 3 (>3.0 x baseline; >3.0 and ≤6.0 x ULN) | Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level |
| Grade 4 (>6.0 x ULN) | Permanently discontinue patient from ceritinib |

| **Worst toxicity (CTCAE 4.03 Grade)*** | **Dose Modifications for ceritinib** |
|---|---|
| Grade 1 (> ULN and <1.5 x ULN) | Maintain dose level |
| Grade 2 (≥1.5 and ≤3.0 x ULN) | Omit dose until resolved to ≤ Grade 1, then:<br>If resolved in ≤7 days, then maintain dose level<br>If resolved in >7 days, then ↓ 1 dose level |
| Grade 3 (>3.0 and ≤6.0 x ULN) | Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level |
| Grade 4 (>6.0 x ULN) | Permanently discontinue patient from ceritinib |
| **GASTROINTESTINAL** | |
| **Diarrhea**** | |
| Grade 1 | Maintain dose level but adjust anti-diarrhea treatment |
| Grade 2 (despite maximal anti-diarrheal medication) | Omit dose until resolved to ≤ Grade 1, then maintain dose level.<br>If diarrhea returns as ≥ Grade 2, then omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level |
| Grade 3 (despite maximal anti-diarrheal medication) | Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level |
| Grade 4 (despite maximal anti-diarrheal medication) | Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level |
| **Nausea***** | |
| Grade 1 or 2 | Maintain dose level but adjust anti-emetic treatment |
| Grade 3 (despite standard anti-emetics) | Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level |
| **Vomiting***** | |
| Grade 1 | Maintain dose level but adjust anti-emetic treatment |
| Grade 2 (despite standard anti-emetics) | Omit dose until resolved to ≤ Grade 1, then maintain dose level.<br>If vomiting returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then ↓ 1 dose level. |
| Grade 3 (despite standard anti-emetics) | Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level |
| Grade 4 (despite standard anti-emetics) | Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level |
| **METABOLIC** | |
| Any Grade **hypophosphatemia** | Treatment with phosphate supplements as clinically indicated and maintain dose level |
| Persistent **hyperglycemia** (glucose >250 mg/dL) despite optimal anti-hyperglycemic therapy | Omit dose until hyperglycemia is adequately controlled, then resume ceritinib at ↓ 1 dose level<br>If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue patient from ceritinib. |
| **GENERAL DISORDERS** | |
| **Fatigue (asthenia)** | |
| Grade 1 or 2 | Maintain dose level |
| Grade 3 | If grade 3 fatigue resolves to Grade 2 in ≤7 days, maintain dose level<br>If grade 3 fatigue lasts >7 days, omit dose until resolved to ≤ Grade 2 and then ↓ dose level |
| **PULMONARY** | |
| Notes:<br>• 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.<br>• During evaluation of potential grade 2, 3, and 4 pneumonitis, if an infectious etiology is confirmed (i.e., pneumonia) and pneumonitis is excluded, then consider resuming ceritinib at current dose level after the pneumonia resolves. | |

| **Worst toxicity (CTCAE 4.03 Grade)*** | **Dose Modifications for ceritinib** |
|---|---|
| **PNEUMONITIS** | |
| Any Grade treatment-related ILD/pneumonitis | Permanently discontinue patient from ceritinib |
| **CARDIAC** | |
| **Electrocardiogram QT corrected (QTc) interval prolonged** | |
| Grade 1 (QTc 450-480 ms)<br>Grade 2 (QTc 481-500 ms) | Maintain dose level |
| Grade 3 (QTc ≥501 ms on at least two separate ECGs) | Omit dose until QTc is less than 481 ms, then ↓ 1 dose level<br><br>- Assess the quality of the ECG recording and the QT value and repeat if needed<br><br>Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTc < 481 ms<br>In addition:-Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment<br>- Review concomitant medication use for drugs with the potential to increase the risk of drug exposure related to QT prolongation<br>- Consider collecting a time-matched PK sample and record time and date of last study drug intake<br><br>After resumption of dosing:<br>-Repeat ECGs 7 days after dose resumption for all patients who had therapy interrupted due to QTc ≥ 501 ms. |
| Grade 4 (QTc ≥501 or >60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia) | Permanently discontinue patient from ceritinib |
| **Bradycardia** | |
| Grade 1 or 2 | Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥60 bpm<br>Evaluate concomitant medications known to cause bradycardia, and adjust the dose of ceritinib. |
| Grade 3<br>Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension) | Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥60 bpm<br>If the concomitant medication can be adjusted or discontinued, resume ceritinib at ↓ 1 dose level with frequent monitoring |
| Grade 4 (in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension) | Permanently discontinue ceritinib. |
| * Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All dose modifications should be based on the worst preceding toxicity.<br>** 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.<br>***LFTs include albumin, ALT, AST, total bilirubin, alkaline phosphatase and GGT<br>**** 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 6.3.4.5)<br>***** 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) | |

### 6.3.4 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific study drug induced toxicities are provided in sub-sections below.

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

#### 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, laboratory 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.

Hematopoietic growth factors (e.g., erythropoietins, G-CSF, and GM-CSF) are not to be administered prophylactically. Use of these drugs should be reserved to patients with severe neutropenia and anemia as per the labeling of these agents.

#### 6.3.4.2 Guidelines for the follow-up of laboratory liver abnormalities

In patients with any clinically relevant laboratory liver abnormality, as defined below, hepatic toxicity monitoring must include **ALL** of the following liver function tests (LFTs): albumin, 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 patient 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/bilirubin increase to grade 3 or 4, LFTs must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 (or to baseline). Thereafter monitoring must be continued every other week (or more frequently if clinically indicated) for 4 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 ceritinib 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).

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

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

- For patients with normal ALT 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 or hepatocellular liver injury).

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

- Laboratory tests should include ALT, AST, albumin, creatine 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.
- Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
- 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 8.3.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

Refer to Table 6-4.

#### 6.3.4.3 Guidelines for the follow-up of laboratory renal abnormalities

In case of any occurrence of serum creatinine results of 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.

#### 6.3.4.4 Guidelines for monitoring pneumonitis (interstitial lung disease)

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 in Table 6-3.

#### 6.3.4.5 Management of study treatment-induced diarrhea

Diarrhea is among the most frequently reported AEs following treatment with ceritinib, and patients must therefore be closely monitored for the appearance of this AE. The investigator should also 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 practices 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 orally, 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 IV fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg sub-cutaneous 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 in Table 6-3.

#### 6.3.4.6 Guidelines for the treatment of study treatment -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 also 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 practices and the investigator's best judgment. For moderately emetogenic drugs, such as ceritinib, International Guidelines for anti-emetic treatment recommend early treatment with 5-HT3-receptor antagonists (5-HT3RAs). Section 6.4.1.2 provides additional details on anti-emetic use. Dose adaptation of ceritinib in case of treatment related nausea and/or vomiting must follow the guidelines presented above in Table 6-3.

#### 6.3.4.7 Guidelines for treatment of hypophosphatemia

In the phase I study [CLDK378X2101], as of 31-Oct-2013, there were 9 cases of grade 3 hypophosphatemia in all dose groups, one of which was a DLT that contributed to the MTD determination – this patient was able to continue ceritinib at the same dose. One patient in the 750 mg group had 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.

#### 6.3.4.8 Guidelines for the follow-up of laboratory pancreatic abnormalities

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

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

Patients who discontinue study treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 3 weeks). Refer to Table 6-4.

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

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

**Table 6-4 Follow-up evaluations for selected toxicities**

| Toxicity | Follow-up evaluation* |
|---|---|
| Investigations (hematologic) | **Febrile neutropenia, neutropenia or thrombocytopenia ≥ CTCAE Grade 3**<br>Test weekly (or more frequent) until ≤ Grade 2<br>Subsequent monitoring must be performed every cycle (4 weeks) |
| Investigations (hepatic) | **Total bilirubin/AST/ALT Grade 2:** (patients with liver metastasis and grade 2 AST/ALT at baseline, increased monitoring required for grade 3 ALT/AST. Follow guidelines for grade 3 or 4 AST/ALT<br>Test weekly (or more frequently) until ≤ Grade 1<br>Thereafter, continue to test every 2 weeks (or more frequently) for 2 cycles (8 weeks)<br>If no recurrence of ≥ Grade 2 event, continue monitoring every cycle (4 weeks)<br>**Total bilirubin/ALT/AST ≥ Grade 3:**<br>Test weekly (or more frequent) until ≤ Grade 1<br>Thereafter, continue to test every 2 weeks (or more frequently) for 4 cycles (16 weeks)<br>If no recurrence of ≥ grade 2 event, continue monitoring every cycle (4 weeks)<br>**Discontinuation due to liver toxicity:**<br>Test weekly (or more frequent) until ≤ Grade 1 or stabilization |
| Investigations (renal) | **Serum creatinine Grade 2:**<br>Test weekly (or more frequent) until Grade 1<br>Thereafter, test every cycle (4 weeks)<br>**Serum creatinine ≥ Grade 3:**<br>Test twice weekly (or more frequent) until ≤ Grade 1<br>Thereafter, test every cycle (4 weeks) |
| Investigations (pancreatic) | **Amylase/lipase ≥ Grade 3:**<br>Test weekly (or more frequently) until ≤ Grade 1. After resumption of dosing, continue to test weekly for one additional cycle (4 weeks). If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle (4 weeks). |
| *Note: this table refers to the evaluation schedule only. Refer to Table 6-3 for dose modifications required for applicable toxicities | |

### 6.3.5 Anticipated risks and safety concerns of the study drug

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 6.3.2. Refer to preclinical toxicity and or clinical data found in the [Investigator's Brochure].

## 6.4 Concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted (see Section 6.4.1 and Section 6.4.2), except as specifically prohibited (see Section 6.4.3).

The patient must be told to notify the investigational site about any new medications he/she takes after the start of study treatment. All medications including herbal/natural medications

(excluding study treatment and prior antineoplastic treatments and blood transfusions), surgeries and procedures (including physical therapy) administered within 30 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 6.4.3.6), food and or vitamin supplements. Patients taking chronic medications should be maintained on the same dose and schedule throughout the study period, if medically feasible.

### 6.4.1 Permitted concomitant therapy

In addition to receiving the study treatment, all patients should receive best supportive care (BSC), as per standard local practice for the treatment of pre-existing medical conditions or adverse events that may arise during the study. BSC is defined as drug or non-drug therapies, nutritional support, physical therapy, or any other treatment alternative that the investigator believes to be in the patient's best interest, but excluding other antineoplastic treatments.

Pain medication to allow the patient to be as comfortable as possible, nutritional support or appetite stimulants (e.g., megestrol), and oxygen therapy and blood products or transfusions will be allowed unless otherwise prohibited in Section 6.4.3.

#### 6.4.1.1 Bisphosphonates

The use of bisphosphonates regardless of indication is allowed 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 and the result of the evaluation should be clearly documented in the patients' source documentation.

No drug-drug interaction is expected between ceritinib and bisphosphonates as the two drugs are eliminated through different elimination pathways. Bisphosphonates are not inhibitors of human CYP450 enzymes involved in the metabolism of ceritinib and do not undergo metabolism *in vivo*. The same guidelines apply to the use of denosumab for the treatment of bone metastatic disease.

#### 6.4.1.2 Antiemetics

Use of antiemetics is allowed. Prophylactic antiemetics should be started only once the patient experiences nausea or vomiting and at the discretion of the investigator. It is recommended that patients use drugs that do not cause QT prolongation. Note that some anti-emetics have a known risk for Torsade de Pointes (TdP) (Appendix P).

#### 6.4.1.3 Oral antidiabetics

Patients who develop diabetes mellitus during the study should be treated according to the ADA (American Diabetes Association) guidance. It is recommended to start treatment with glimepiride, glibenclamide or metformin. Patients receiving oral antidiabetics which are predominantly metabolized by CYP2C9 and CYP2C8, including but not limited to,

repaglinide, rosiglitazone, glipizide and tolbutamide, must be carefully monitored for hypoglycemia.

### 6.4.2 Permitted concomitant therapy requiring caution and/or action

#### 6.4.2.1 Corticosteroids

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

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

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

#### 6.4.2.2 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 BYP2A6 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 14-14 of Appendix P). Duration of concomitant treatment should be kept as short as possible, or completely avoided whenever possible. Patients receiving such medications must be monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and may require dose titration or adjustment. Note that co-administration of ceritinib with strong inhibitors or inducers of CYP3A4/5 is prohibited (Section 6.4.3.4).

Concomitant treatment of ceritinib with medications known to be metabolized by CYP2C9 and CYP3A4 is allowed with caution, except for drugs which have narrow therapeutic index/sensitive substrates for these CYP isoforms (Section 6.4.2.2 and Table 14-14 of Appendix P).

#### 6.4.2.3 Non-enzyme inducing anti-epileptic drugs

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

#### 6.4.2.4 Palliative radiotherapy and surgery

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. If palliative radiotherapy is initiated after start of ceritinib treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be assessed and documented. Patients who develop progressive disease but are still deriving clinical benefit from ceritinib therapy, as determined by the Investigator, may undergo radiotherapy and/or surgical resection as palliative localized therapy to treat metastatic lesions. Ceritinib should be held for at least 4 days prior to radiotherapy and at least 1 day prior to surgery. Ceritinib may be resumed ≥ 3 days after completing radiotherapy or minor surgery, and ≥ 2 weeks after major surgery.

#### 6.4.2.5 Gastric protection agents

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

### 6.4.3 Prohibited concomitant therapy

#### 6.4.3.1 Other investigational and anti-neoplastic therapies

Concurrent use of other investigational drugs is not permitted.

Anticancer therapy (chemotherapy, targeted therapy, biologic or radiation therapy (that includes > 30% of the bone marrow reserve and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study.

#### 6.4.3.2 Warfarin and coumadin derivatives

Therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulants are not permitted. Ceritinib is an inhibitor of CYP2C9, the major metabolizing enzyme of warfarin. A clinically relevant increase in warfarin exposure is possible. Anticoagulants not derived from warfarin are allowed (eg, dabigatran, rivaroxaban, apixaban).

#### 6.4.3.3 Enzyme inducing anti-epileptic drug (EIAED)

Use of EIAEDs is not permitted. Refer to Table 14-15 of Appendix P 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 ceritinib treatment.

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.

#### 6.4.3.4 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 study. Refer to Table 14-13 of Appendix P for a list of these medications. Please note that this list may not be comprehensive.

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

Ceritinib is a potent inhibitor of drugs metabolized by the CYP2C9 and CYP3A4/5 *in vitro*. Because of the potential risk for drug-drug interactions, using concomitant medications known to be metabolized by these enzymes and that have a narrow therapeutic index is not permitted concomitantly with ceritinib. Refer to Table 14-13 of Appendix P and Table 14-14 of Appendix P for a list of these medications. Please note that this list may not be comprehensive.

#### 6.4.3.6 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 ceritinib treatment.

#### 6.4.3.7 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. However, there were no ceritinib -related effects *in vivo* in monkeys at doses as high as 100 mg/kg (human equivalent dose (HED) of 1950 mg).

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in an open-label, dose-escalation, and expansion study [CLDK378X2101]. A total of 304 patients were treated with ceritinib doses ranging from 50 to 750 mg with 255 patients treated with ceritinib 750 mg. One of 304 patients (<1%) was found to have a QTc >500 msec and 10 patients (3.3%) had an increase from baseline QTc >60 msec. A central tendency analysis of the QTc data at average steady-state concentrations demonstrated that the upper bound of the 2-sided 90% CI for QTc was 16 msec at ceritinib 750 mg. A PK/PD 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 14-16 of Appendix P 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 and enrollment

### 6.5.1 Patient numbering

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

### 6.5.2 Treatment assignment and randomization

Not applicable.

### 6.5.3 Treatment blinding

This is an open-label study.

## 6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) 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.

Patients will be provided with an adequate supply of study drug for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Patients will receive ceritinib on an outpatient basis. The investigator shall provide the patient with instructions for ceritinib administration according to the protocol.

### 6.6.1 Study drug packaging and labeling

Ceritinib will be supplied as 150 mg capsules (refer to Table 6-5).

Medication labels will comply with US legal requirements and are printed in the local language. The label contains ceritinib identifying information (e.g., formulation, batch number, and expiration date), the patient number (to be entered by the investigator or designee) and storage conditions.

**Table 6-5 Packaging and labeling**

| Study treatments | Packaging | Labeling (and dosing frequency) |
|---|---|---|
| ceritinib (LDK378) | Capsules or tablets (150 mg) in bottles or blisters | Labeled as LDK378<br>Dosing frequency: once-a-day, 28 days |

### 6.6.2 Drug supply and storage

Each site will be supplied by Novartis with oral ceritinib. Study drug must be received by a designated person 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, ceritinib should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure]. These instructions should also be made clear to the patient for storage and self-administration of ceritinib at home.

Site staff will be responsible for managing adequate re-supplies for ceritinib.

### 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 must be captured in the source document at each patient visit.

#### 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 Novartis or designee.

### 6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

# 7 Visit schedule and assessments

## 7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column). Every effort must be made to follow the schedule of assessments within the ±4 days.

**Table 7-1 Visit evaluation schedule**

| Visit Number | Category | Reference to assessment | Screening phase | Treatment Phase | | | | | | Post treatment follow-up phase | Survival phase |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Screening | C1 | | C2 | | Subsequent cycles | EOT | Safety follow up | Survival FU |
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 777 | 501 | 701 |
| Cycle days[1] | | | -28 to -1 | 1 | 15 | 1 | 15 | 1 | | EOT + 30 (±4) days | EOT + every 3 months[2] |
| **ALL PATIENTS** | | | | | | | | | | | |
| **INFORMED CONSENT** | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | |
| Informed consent | D | 7.1.1 | X | | | | | | | | |
| **PATIENT HISTORY** | | | | | | | | | | | |
| Demography | D | 7.1.1.3 | X | | | | | | | | |
| Inclusion/exclusion criteria | S | 5.2 & 5.3 | X | | | | | | | | |
| Eligibility checklist | S | 7.1.1.1 | X | | | | | | | | |
| End of phase disposition | D | 7.1.3.1 | | | | | | | X | | |
| Relevant medical history/ current medical conditions | D | 7.1.1.3 | X | | | | | | | | |
| Diagnosis and Extent of cancer | D | 7.1.1.3 | X | | | | | | | | |
| Prior anti-neoplastic therapy | D | 7.1.1.3 | X | | | | | | | | |
| **PHYSICAL EXAMINATION** | | | | | | | | | | | |
| Physical examination | S | 7.2.2.1 | X | X[4] | | X | | X | X | | |
| Vital signs | D | 7.2.2.2 | X | X[4] | | X | | X | X | | |

| Visit Number | Category | Reference to assessment | Screening phase | Treatment Phase | | | | | | Post treatment follow-up phase | Survival phase |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Screening | C1 | | C2 | | Subsequent cycles | EOT | Safety follow up | Survival FU |
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 777 | 501 | 701 |
| Cycle days[1] | | | -28 to -1 | 1 | 15 | 1 | 15 | 1 | | EOT + 30 (±4) days | EOT + every 3 months[2] |
| Height | D | 7.2.2.3 | X | | | | | | | | |
| Weight | D | 7.2.2.3 | X | X[4] | | X | | X | X | | |
| ECOG performance status | D | 7.2.2.4 | X | X[4] | | X | | X | X | | |
| **IMAGING AND OTHER ASSESSMENTS** | | | | | | | | | | | |
| Cardiac imaging (MUGA/ECHO) | D | 7.2.2.7.2 | X | If clinically indicated | | | | | | | |
| ECG | D | 7.2.2.7.1 | X | X[4] | | X | | X | X | | |
| **LABORATORY ASSESSMENTS** | | | | | | | | | | | |
| Hematology | D | 7.2.2.5.1 | X | X[4] | X | X | X | X | X | | |
| Biochemistry (including liver function tests) | D | 7.2.2.5.2 | X | X[4] | X | X | X | X | X | | |
| Thyroid Function | D | 7.2.2.5.3 | X | X[4] | | | | Every 3 cycles starting from C3D1 or if clinically indicated | X | | |
| Cardiac enzymes | D | 7.2.2.7.3 | X | If clinically indicated | | | | | | | |
| Coagulation | D | 7.2.2.5.4 | X | X[4] | If clinically indicated | | | | | | |
| Urinalysis | D | 7.2.2.5.5 | X | X[4] | | X | | X | X | | |
| Pregnancy test[6] | D | 7.2.2.5.6 | X | X[4] | | X | | X | X | | |
| **SAFETY** | | | | | | | | | | | |
| Prior and concomitant medications | D | 6.4 | X | Continuous | | | | | | X | |
| Surgical and medical procedures | D | 6.4 | X | Continuous | | | | | | X | |

| Visit Number | Category | Reference to assessment | Screening phase | Treatment Phase | | | | | | Post treatment follow-up phase | Survival phase |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Screening | C1 | | C2 | | Subsequent cycles | EOT | Safety follow up | Survival FU |
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 777 | 501 | 701 |
| Cycle days[1] | | | -28 to -1 | 1 | 15 | 1 | 15 | 1 | | EOT + 30 (±4) days | EOT + every 3 months[2] |
| Adverse events | D | 8.1 | X | Continuous | | | | | | X | |
| **DRUG ADMINISTRATION AND OTHERS** | | | | | | | | | | | |
| ceritinib administration | D | 6.1.1 | | Daily | | | | | | | |
| Survival | D | 7.1.4.3 | | | | | | | | | X |
| **ADDITIONAL EFFICACY ASSESSMENTS** | | | | | | | | | | | |
| **SOLID TUMOR** | | | | | | | | | | | |
| Physical examination for measurement of superficial disease (only if present) [9] | D | 7.2.1.1.1 | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) | | | | | X | | |
| Radiological tumor assessment/ response assessment (MRI/CT Scans [3, 5, 7, 8]) | D | 7.2.1.1.4 | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) | | | | | X | | |
| Cancer Antigen-125 (for ovarian cancer only) | D | 7.2.1.1.2 | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) | | | | | X | | |
| Prostate-specific antigen (PSA) (for prostate cancer only) | D | 7.2.1.1.3 | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) | | | | | X | | |
| **LYMPHOMA** | | | | | | | | | | | |
| Examination for enlarged spleen or liver | D | 7.2.1.2.1 | X | To confirm response of CR | | | | | X | | |
| Physical examination for measurement of superficial disease and B symptoms [9] | D | 7.2.1.2.2 | X | Day 1 of every cycle (±4 days) after first dose of study drug | | | | | X | | |

| Visit Number | Category | Reference to assessment | Screening phase | Treatment Phase | | | | | | Post treatment follow-up phase | Survival phase |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Screening | C1 | | C2 | | Subsequent cycles | EOT | Safety follow up | Survival FU |
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 777 | 501 | 701 |
| Cycle days[1] | | | -28 to -1 | 1 | 15 | 1 | 15 | 1 | | EOT + 30 (±4) days | EOT + every 3 months[2] |
| Radiological tumor assessment/ response assessment (MRI/CT Scans [3, 5, 7, 8]) | D | 7.2.1.2.3 | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) | | | | | X | | |
| Bone Marrow Biopsy or aspirate | D | 7.2.1.2.4 | | To confirm response of CR[10] | | | | | | | |
| Serum protein electrophoresis (SPEP) | D | 7.2.1.2.5 | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) only if abnormal M-protein detected at baseline | | | | | X | | |
| PET Scan | D | 7.2.1.2.6 | | To confirm response of CR (can be part of CT/PET) | | | | | | | |
| **SYMPTOMATIC MULTIPLE MYELOMA** | | | | | | | | | | | |
| Skeletal Survey | D | 7.2.1.3.1. | X | If clinically indicated | | | | | | | |
| Urine protein electrophoresis (UPEP)[7] | D | 7.2.1.3.2. | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) | | | | | X | | |
| Free light chain[7] | D | 7.2.1.3.3. | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) | | | | | X | | |
| Serum protein electrophoresis (SPEP)[7] | D | 7.2.1.3.4. | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) | | | | | X | | |
| MRI/CT Scans (For plasmacytoma Only) | D | 7.2.1.3.5. | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) | | | | | | | |
| Bone Marrow Biopsy or aspirate | D | 7.2.1.3.6. | X | To confirm response of CR | | | | | | | |
| **Chronic Lymphocytic Leukemia (CLL)** | | | | | | | | | | | |
| Examination for enlarged spleen or liver | D | 7.2.1.2.1 | X | To confirm response of CR | | | | | | | |

| Visit Number | Category | Reference to assessment | Screening phase | Treatment Phase | | | | | | Post treatment follow-up phase | Survival phase |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Screening | C1 | | C2 | | Subsequent cycles | EOT | Safety follow up | Survival FU |
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 777 | 501 | 701 |
| **Cycle days[1]** | | | **-28 to -1** | **1** | **15** | **1** | **15** | **1** | | **EOT + 30 (±4) days** | **EOT + every 3 months[2]** |
| Physical examination for measurement of superficial disease and B symptoms [9] | D | 7.2.1.2.2 | X | Day 1 of every cycle (±4 days) after first dose of study drug | | | | | X | | |
| Radiological tumor assessment/ response assessment (MRI/CT Scans [3, 5, 7, 8]) | D | 7.2.1.2.3 | X | Every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) | | | | | X | | |
| Bone Marrow Biopsy or aspirate | D | 7.2.1.2.4 | | To confirm response of CR | | | | | | | |
| Peripheral Blood for CBC differential and blast count | D | 7.2.1.4.1 | X | X | X | X | X | X | X | | |
| Physical examination for assessment of Extramedullary disease or Organomegaly (if present) | D | 7.2.1.4.3 | X | X | X | X | X | X | X | | |
| **LEUKEMIA, MDS, MF, PV and ET** | | | | | | | | | | | |
| Peripheral Blood for CBC differential and blast count | D | 7.2.1.4.1 | X | X | X | X | X | X | X | | |
| Physical examination for assessment of Extramedullary disease or Organomegaly (if present) | D | 7.2.1.4.3 | X | X | X | X | X | X | X | | |
| Bone Marrow Biopsy or aspirate | D | 7.2.1.4.2 | X | To confirm response of CR or if clinically indicated | | | | | | | |
| Assessments of chromosomal abnormalities/Karyotype | S | 7.2.1.4.4 | X[11] | | | | | | | | |

| Visit Number | Category | Reference to assessment | Screening phase | Treatment Phase | | | | | | Post treatment follow-up phase | Survival phase |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Screening | C1 | | C2 | | Subsequent cycles | EOT | Safety follow up | Survival FU |
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 777 | 501 | 701 |
| Cycle days[1] | | | -28 to -1 | 1 | 15 | 1 | 15 | 1 | | EOT + 30 (±4) days | EOT + every 3 months[2] |
| Evaluation of transfusion dependency | D | 7.2.1.4.5 | X | X | X | X | X | X | X | | |

[1] A complete cycle is defined as 28 days.
[2] Additional survival assessments may be performed outside the 3 months follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.
[3] Tumor assessments at EOT are required for patients who discontinue study treatment before the first scheduled post-screening tumor assessment and for patients whose previous tumor assessment did not demonstrate PD and was done at least 8 weeks (± 4 days) prior to end of treatment visit.
[4] These assessments should be performed only if the screening assessment occurred > 4 days from Cycle 1 Day 1. The patient must continue to meet all eligibility criteria on C1D1, as they did during the screening period prior to first dose.
[5] Tumor assessments include CT/MRI of the chest abdomen and pelvis at all timepoints. Tumor assessments are described in Section 7.2.1
[6] Women of childbearing potential must undergo a serum pregnancy test at screening and EOT. Women of child-bearing potential will undergo a monthly urine pregnancy tests during the study.
[7] For patients who have a response of PR or greater, a confirmation assessment must be performed at least 4 weeks after the initial observation.
[8] The frequency of disease assessment may be reduced to every 12 weeks for patients who have at least 4 post baseline disease assessments and are clinically stable.
[9] Skin lesions should be documented using a digital camera (color photography) in clear focus showing the ruler or calipers and the corresponding measurement in such a way that the size of the lesion(s) can be determined from the photograph
[10] Only to confirm complete responses in patients with bone marrow tumor involvement prior to study treatment
[11] Information on the patient's chromosomal abnormalities/karyotyping based on documented history prior to study entry must be present in his/her source documents. Additional testing to confirm these response categories will not be required and should be done at the discretion of the attending physician

[redacted]

### 7.1.1 Screening

For the purpose of this study, genomic profiling is not considered part of screening. This study is intended for patients who have already had genomic profiling of their tumors in a CLIA certified laboratory [redacted] Eligibility is based on [redacted] study as assessed in the local, CLIA certified laboratory. The results of this testing must be known prior to signing the ICF and before formal screening begins. Laboratory results must be 'unambiguous' or 'unequivocal'. Results that state 'ambiguous' or 'equivocal' imply low probability that genetic deregulation is truly present and an important driver of patient's tumor. Written informed consent must be obtained before any study specific assessments are performed, including screening. All screening evaluations must be performed as closely as possible to the beginning of treatment and never more than 28 days prior to starting study drug dose of ceritinib to confirm patient's eligibility.

Upon signing the Informed Consent Form (ICF), a patient will be assigned a 7-digit patient number.

[redacted]

An archival or fresh tumor sample may not be required if the patient has had their genomic profiling performed at the same laboratory that will be used for confirmatory analysis, and the patient consents to allow Novartis to use that data as their baseline molecular analysis results.

[redacted] ALK positivity as assessed by IHC or FISH are allowed.

Patients who fail to start on treatment may be re-screened.

Disease assessments (per RECIST 1.1 or appropriate hematologic response criteria) must be performed within 28 days prior to enrollment and will be assessed locally by the investigator.

When information from procedures (for example imaging assessments) that may have been previously performed as part of the patient's routine disease care (prior to enrolling in the trial) is allowed to be used to satisfy inclusion criteria, if it was performed <28 days before the start of study treatment.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure.

For details of assessments, refer to Table 7-1 and Section 7.2.

#### 7.1.1.1 Eligibility screening

Subject's mutational status will be confirmed by Novartis or designee prior to the subject receiving the first dose of study drug.

#### 7.1.1.2 Information to be collected on screening failures

Patients who sign the ICF, but are not enrolled for any reason will be considered a screen failure. A patient who is enrolled but does not start treatment is not considered a screen failure.

For screen failure patients, the reason for not proceeding with enrollment will be entered on the Screening Log eCRF. No waivers will be granted.

The following eCRFs must be completed for screening failure patients:

- Screening Log eCRF page (including reason for not being started on treatment)
- Informed Consent
- Demography
- Serious Adverse Event after signing the ICF - see Section 8 for SAE reporting details.

#### 7.1.1.3 Patient demographics and other baseline characteristics

Patient information to be collected at screening will include:

- [redacted]
- Demographic data (age, gender, race)
- Diagnosis and Extent of Cancer
- Relevant Medical History (e.g., important medical, surgical, and allergic conditions from the patient's medical history, which could have an impact on the patient's evaluation)/Current Medical Conditions (e.g., all relevant current medical conditions which are present before the first dose of study drug is administered).
  - Cancer-related conditions and symptoms which are recorded on the Medical History eCRF should include the grade
- Prior Anti-neoplastic Medications
- Prior Anti-neoplastic Radiotherapy
- Prior Anti-neoplastic Surgery
- All other medications and non-drug therapies (including physical therapy, oxygen and blood transfusions) administered to the patient within 28 days prior to the first dose of study drug) must be reported on the appropriate eCRFs
- Furthermore the following assessments will be performed to assess the eligibility of the patient:
  - Physical Examination (See Section 7.2.2.1)
  - Vital signs (See Section 7.2.2.2)
  - Height, weight (See Section 7.2.2.3)

- ECOG performance status (See Section 7.2.2.4)
- Laboratory evaluations (e.g., hematology, coagulation, biochemistry, urinalysis, liver function monitoring) (See Section 7.2.2.5)
- [redacted]
- Serum pregnancy (See Section 7.2.2.5.6)
- Cardiac assessment (See Section 7.2.2.7)
- Disease evaluations (See Section 7.2.1)
- Radiological assessments (e.g., CT scan) if clinically indicated (See Section 7.2.1)

### 7.1.2 Treatment period

Patients will be treated with ceritinib (750 mg, orally, once-a-day,) until disease progression, unacceptable toxicity, death or discontinuation from the study treatment due to any other reason.

For details of safety and efficacy assessments, refer to Table 7-1 and Section 7.2.

- Visits and associated assessments that occur ± 4 days from the scheduled date (except for cycle 1 Day1 where no visit window is allowed) will not constitute protocol deviations.
- The cycle length is 28 days. Day 1 of subsequent cycles will be calculated from cycle 1, day 1.
- Disease Assessments (per RECIST or appropriate hematological response criteria) must be performed every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle), until disease progression or end of treatment, whichever occurs first. The frequency of disease assessment may be reduced to every 12 weeks for patients who have at least 4 post-baseline disease assessments and are clinically stable (except AML patients).
- Laboratory assessments performed as part of the screening evaluations and within 4 days of the first dose of study treatment, are not required to be repeated on the first dosing day.
- [redacted]

### 7.1.3 End of treatment visit, including premature withdrawal and study discontinuation visit

#### 7.1.3.1 End of treatment (EOT) visit

Patients who completely discontinue study treatment should be scheduled for an End of Treatment (EOT) visit within 7 days following the date study treatment is permanently discontinued, at which time all of the assessments listed for the EOT visit will be performed. For details of assessments, refer to Table 7-1. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit.

An End of Treatment Phase Disposition eCRF page should be completed, giving the date and reason for stopping the study treatment. If a study withdrawal occurs, or if the patient fails to

return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment Phase Disposition eCRF page.

End of treatment/Premature withdrawal visit is not considered as the end of the study.

For patients with a best response of SD or better who discontinued study treatment due to disease progression, an optional tumor sample should be obtained for genomic analysis.

[redacted]

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.

#### 7.1.3.2 Criteria for premature patient withdrawal (EOT phase completion)

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator or by the sponsor at any time.

Premature patient withdrawal refers to the point/time when the patient exits from the study treatment prior to the planned completion of all study treatment administration and/or assessments; at this time, all study drug treatment is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival.

Patients may be withdrawn from the study treatment if any of the following occur:

- Adverse Event
- Lost to follow-up
- Non-compliance with study treatment
- Physician decision
- Pregnancy
- Progressive Disease
- Protocol deviation
- Study terminated by sponsor
- Subject/guardian decision
- Death
- In addition to the general withdrawal criteria, the following **study specific criteria** will also require study treatment discontinuation:
  - Adjustments to study treatment that result in discontinuation. Please refer to Section 6.3
  - Use of prohibited medication. Please refer to Section 6.4.3

### 7.1.4 Follow up period

#### 7.1.4.1 Safety follow up

All patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations (i.e., assessment of AEs and/or SAEs, concomitant medications) for 30 days after the last dose of study treatment. Patients whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed at least once a week for 4 weeks and subsequently at 4-weeks intervals until resolution or stabilization of the event, whichever comes first.

If patients refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the patient should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.).

#### 7.1.4.2 Efficacy follow-up

Not applicable.

#### 7.1.4.3 Survival follow-up

Survival information will be collected every 3 months until 2 years after the last patient has enrolled in the study regardless of treatment discontinuation reason (except if consent is withdrawn). If the study primary efficacy endpoint is not met, Novartis may decide not to conduct survival follow-up for the study. Additional survival assessments may be performed outside the 3 months follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.

Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

#### 7.1.4.4 Lost to follow-up

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

### 7.1.5 End of post-treatment follow-up (Study phase completion)

Not applicable.

## 7.2 Assessment types

### 7.2.1 Efficacy assessments

The primary efficacy endpoint is clinical benefit rate as defined in Section 10.4. The key secondary efficacy endpoint is overall response rate of PR or greater as defined in Section 10.5. Other secondary endpoints are time from the date of first dose to the date of first

documented disease progression or relapse or death due to any cause, time from the date of first dose to the date of death due to any cause, time from the first documented response to the date first documented disease progression or relapse or death due to any cause, AE rate, and other safety measurements as defined in Section 10. The local investigator's assessment will be used for the analysis and for treatment decision making.

Clinical suspicion of disease progression at any time will require assessment and confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent disease assessments must be performed according to the originally planned schedule from baseline.

#### 7.2.1.1 Solid Tumors

Response will be evaluated, using modified Response Evaluation Criteria in Solid Tumors, based on RECIST 1.1. For complete details, refer to Appendix A.

Clinical evaluation and tumor assessments will be performed as is indicated in Table 7-1, based on physical examination and radiological evaluation. For solid tumors, an assessment of CR or PR using RECIST 1.1 must be confirmed at least 4 weeks after initial observation. If the two assessments differ, the best overall response will be determined as outlined in Table 14-5 of Appendix B.

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

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Definitions for measurable and non-measurable lesions, and criteria for response, should be based on RECIST 1.1 (Appendix A).

##### 7.2.1.1.1 Physical examination for superficial disease

Clinical assessment of any existing superficial lesions (skin nodules and palpable lymph nodes) at screening and at each subsequent tumor assessment must be performed on the same schedule as radiological tumor assessments (see Section 7.2.1.1.4).

Skin lesions should be documented using a digital camera (color photography) in clear focus showing the ruler or calipers and the corresponding measurement in such a way that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

##### 7.2.1.1.2 Cancer Antigen-125 (CA-125)

Cancer Antigen-125 (CA-125) will be used in the assessment of ovarian cancer at screening. Subsequent tumor assessments must be performed on the same schedule as radiological tumor assessments (see Section 7.2.1.1.4).

#### 7.2.1.1.3 Prostate Specific Antigen (PSA)

Prostate Specific Antigen (PSA) will be used in the assessment of prostate cancer at screening. Subsequent tumor assessments must be performed on the same schedule as radiological tumor assessments (see Section 7.2.1.1.4).

#### 7.2.1.1.4 Radiological tumor assessment

At screening and at each subsequent tumor assessment, all patients must have a CT scan with contrast of the Chest/Abdomen and Pelvis. If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.

The same type of CT scan used at screening must be used for all subsequent assessments. MRI with contrast will be allowed only in those cases when CT scan cannot be performed and will be used at baseline and all subsequent assessments in these patients. No modality change would be allowed during the study when assessing overall tumor status. For subsequent scans in the same patient, the radiologist must account for all lesions that were present at screening and must use the same technique as used at screening. If possible, a single radiologist should perform all tumor response evaluations for an individual patient. Only in exceptional cases when during the study a patient develops intolerance to the CT scan contrast medium, a CT scan without contrast will be acceptable to avoid modality change. At screening, tumor assessments should preferably be performed ≤ 4 days prior to the first dose of ceritinib, however tumor assessments ≤ 28 days prior to first dose of study drug will be acceptable.

Tumor assessments will be performed at screening and every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle). The frequency of disease assessment may be reduced to every 12 weeks for patients who have at least 4 post-baseline disease assessments and are clinically stable.

### 7.2.1.2 Lymphoma

Response will be evaluated, using modified criteria for malignant lymphoma Cheson (Appendix B) and Ann Arbor Staging Classification (Appendix C).

Clinical evaluation and tumor assessments will be performed periodically, as is indicated in Table 7-1, based on evaluation of spleen and liver, physical examination for superficial disease and B symptoms, radiological evaluation, Serum Protein electrophoresis (SPEP), core bone marrow biopsy (only to confirm complete responses in patients with bone marrow tumor involvement prior to study treatment), and positron emission tomography (PET) (only to confirm complete responses in patients where PET was used for study entrance).

#### 7.2.1.2.1 Enlarged spleen and liver

The presence of enlarged spleen or liver before start of treatment on the basis of CT scan (or MRI scan) should be recorded on the corresponding eCRF at baseline, and reassessed if the patient has a radiological CR.

A maximum four of the largest dominant measurable nodules representing all involved anatomic locations should be selected as splenic and hepatic index lesions to be measured.

All other splenic or hepatic nodules (both measurable and non-measurable) are considered as non-index lesions.

#### 7.2.1.2.2 Physical examination for superficial disease and B symptoms

Tumor assessment by physical examination and evaluation of disease related B symptoms (unexplained fever of ≥ 38°C; unexplained, recurrent drenching night sweats; or unexplained loss of >10% body weight within the previous 6 months) will be performed at screening and day 1 of every cycle (±4 days) after first dose of study drug. Refer to Appendix B for specifications and measurement.

Skin lesions should be documented using a digital camera (color photography) in clear focus showing the ruler or calipers and the corresponding measurement in such a way that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

#### 7.2.1.2.3 Radiological tumor assessment

Tumor assessments will be performed at screening, and every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle), until disease progression or end of treatment, whichever occurs first. The frequency of disease assessment may be reduced to every 12 weeks for patients who have at least 4 post-baseline disease assessments and are clinically stable.

At screening and at each subsequent tumor assessment, all patients must have a CT scan with contrast of the Chest/Abdomen and Pelvis. If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.

MRI with contrast will be allowed only in those cases when CT scan cannot be performed and will be used at baseline and all subsequent assessments in these patients. No modality change would be allowed during the study. when assessing overall tumor status. For subsequent scans in the same patient, the radiologist must account for all lesions that were present at screening and must use the same technique as used at screening. If possible, a single radiologist should perform all tumor response evaluations for an individual patient. Only in exceptional cases when during the study a patient develops intolerance to the CT scan contrast medium, a CT scan without contrast will be acceptable to avoid modality change. At screening, tumor assessments should preferably be performed ≤ 4 days prior to the first dose of ceritinib, however tumor assessments ≤ 28 days prior to first dose of study drug will be acceptable.

All patients should have at least one site of measurable nodal disease > 2.0 cm in the longest transverse diameter and clearly measurable in at least two perpendicular dimensions, as determined by CT scan (MRI is allowed only if CT scan cannot be performed). Complete guidance for selecting index lesions is provided in Appendix A. Index lesions will be measured and recorded at baseline and during the course of the study. They should be selected

on the basis of their size and suitability for accurate repeat measurements. Skin lesions, if the area is ≥ 2 cm in at least one diameter, must be histologically confirmed for lymphoma involvement (the site must document the histological confirmation (yes or no) to the corresponding eCRF) and photographed (color photography using digital camera).

A sum of the product of diameters (SPD) for lesions measured prior to study treatment will be calculated and reported at cycle 1 day 1.

Conventional CT and MRI should be performed with contiguous cuts of 7.5 mm or less in slice thickness. Spiral CT should be performed using a 5 mm or less contiguous reconstruction algorithm (this specification applies to tumors of the chest, abdomen and pelvis).

If a very small lesion cannot be reliably measured because of its size, it is recommended to enter the minimum lesion size (i.e., 5 mm for spiral CT). In other cases where the lesion cannot be reliably measured for reasons other than its size (i.e., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

Any measurable extranodal lesions (organs other than lymph nodes) that resolves from baseline (disappear completely) must be assigned a size of 0 mm when documenting on the corresponding eCRFs. An extranodal lesion must be ≥ 1 cm x 1 cm to be considered measurable. Refer to Appendix A for complete reporting guidelines.

#### 7.2.1.2.4 Bone marrow assessment

Information on the patient's bone marrow involvement based on documented history prior to study entry must be present in his/her source documents. Prior tumor bone marrow involvement should be entered on the corresponding eCRF.

Core bone marrow biopsy or aspirate will not be performed at screening but is required to confirm complete responses (at the first occurrence of radiological and clinical evidence of CR) in patients with bone marrow tumor involvement prior to study treatment who achieve Complete Response based on clinical and radiological evidence. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). Bone marrow biopsy or aspirate should be obtained no later than at the next visit immediately following clinical and radiological evidence of CR (i.e. < 28 days ± 7 days from the date of the radiological assessment, on which the CR is based on).

#### 7.2.1.2.5 Serum Protein electrophoresis (SPEP)

Serum protein electrophoresis (SPEP) will be performed by the local laboratory at screening and on the same schedule as radiological tumor assessments (see Section 7.2.1.2.3) only if abnormal M-protein is detected at screening.

#### 7.2.1.2.6 Positron emission tomography (PET)

The use of Positron emission tomography (PET) is not standard in Novartis Oncology Lymphoma studies. PET evaluations that have been done as standard of care prior to enrollment will be recorded in the eCRF. Repeat PET will be required only for patients who

have responses of CR for the purpose of this study and should be done within +/- 7 days of the CT or MRI to confirm CR. Refer to Appendix B for lesion measurements.

#### 7.2.1.3 Symptomatic multiple myeloma

Response will be evaluated using the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. For complete details, refer to Appendix N.

Clinical evaluation and disease assessments will be performed periodically, as is indicated in Table 7-1, based on a skeletal survey Urine protein electrophoresis (UPEP), Free light chain, Serum Protein electrophoresis (SPEP), bone marrow biopsy, and MRI/CT Scans (For plasmacytoma only).

##### 7.2.1.3.1 Skeletal survey

Skeletal survey will be performed at screening and if clinically indicated as outlined in Table 7-1.

##### 7.2.1.3.2 Urine protein electrophoresis (UPEP)

Urine protein electrophoresis (UPEP) will be performed by the local laboratory at screening, every 8 weeks (±4 days) after first dose of study drug (Day 1 of every odd cycle) and EOT.

##### 7.2.1.3.3 Free Light Chain

Free Light Chain will be performed by the local laboratory at screening and on the same schedule as UPEP assessments (see Section 7.2.1.3.2).

##### 7.2.1.3.4 Serum protein electrophoresis (SPEP)

Serum protein electrophoresis (SPEP) will be performed by the local laboratory at screening and on the same schedule as UPEP assessments (see Section 7.2.1.3.2).

##### 7.2.1.3.5 MRI/CT scans (for plasmacytoma only)

For patients with plasmacytoma, a MRI/CT scan will be performed by the local laboratory at screening and on the same schedule as UPEP assessments (see Section 7.2.1.3.2).

##### 7.2.1.3.6 Bone marrow assessment

Information on the patient bone marrow involvement prior to study entry must be present in his/her source documents. Prior tumor bone marrow involvement should be entered on the corresponding eCRF.

Core bone marrow biopsy is required to confirm Complete Responses (at the first occurrence of radiological and clinical evidence of CR) in patients with bone marrow tumor involvement prior to study treatment who achieve Complete Response based on clinical and radiological evidence. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). Bone marrow biopsy should be obtained no later than at the next visit immediately following clinical and radiological evidence of CR (i.e. < 28 days ± 7 days from the date of the radiological assessment, on which the CR is based on).

#### 7.2.1.4 Leukemia

Response for AML will be evaluated using the revised recommendations of the International Working Group (IWG) as noted in Cheson 2003 (Appendix E). Response for ALL will be evaluated using guidelines adapted from NCCN Guidelines Version 2.2012 (Appendix F). CML will be evaluated using guidelines adapted from NCCN Guidelines Version 3. 2013 (Appendix G). The response for CLL will be evaluated using the revised recommendation of the IWG as noted in Hallek 2008 (Appendix H). The response for myelodysplasia (MDS) will be evaluated using the revised recommendation of the IWG as noted in Cheson 2005 (Appendix L). The response for polycythemia vera (PV) and essential thrombocythemia (ET) will be evaluated using the recommendation of IWG-MRT as noted in Barosi 2013 (Appendix J and Appendix K respectively). The response for myelofibrosis (MF) will be evaluated using IWG-MRT as noted in Tefferi 2013 (Appendix I).

Clinical evaluation and disease assessments for AML, ALL, CML, MDS, PV, ET, and MF will be performed periodically, as is indicated in Table 7-1, based on peripheral blood and bone marrow assessment as well as the presence or absence of extramedullary disease, and organomegaly, and evaluation of transfusion dependency.

Clinical evaluations and disease assessments for CLL will be performed periodically as is indicated in Table 7-1, based on the lymphoma schedule for evaluation of physical examination for superficial disease and B symptoms, radiological evaluation, core bone marrow biopsy (only to confirm complete responses in patients with bone marrow tumor involvement prior to study treatment) and Rai staging criteria (Appendix D). Peripheral blood, and the presence or absence of extramedullary disease and organomegaly will also be performed on the same schedule as other leukemia evaluations as indicated below.

To assess response, the time interval between bone marrow and blood assessments may not exceed 5 days. If the time interval is more than 5 days, response status cannot be assessed at that time point. Regular bone marrow assessments are not required after achieving a CR unless indicated by blood counts or clinical assessments or specified in the protocol.

The response assessment date is defined as the last of all dates of measurements which are required to qualify for a response category within the period listed above. This rule applies also in case of multiple measurements of the same variable. In case of relapse, the first of all measurement dates associated with a disease assessment will be used as assessment date. The assessment date will be used for the derivation of the time-to-event endpoints.

##### 7.2.1.4.1 Peripheral blood evaluation for CBC

Peripheral blood evaluations will be performed by the local laboratory at screening, Day 1 and Day 15 of Cycles 1 and 2, at Day 1 of each subsequent cycle, and at EOT.

Peripheral blood evaluation for CBC will be taken from the same sample and include evaluation of blast, neutrophil, and platelet cell count.

##### 7.2.1.4.2 Bone Marrow assessment

Bone marrow will be assessed for blast cell count at screening, to confirm response of CR or if clinically indicated.

Percent blast cell count will be determined by cytological examination. This assessment can be performed in terms of bone marrow aspirate and/or biopsy. Results from these tests are considered to be interchangeable to assess blasts counts. In case both aspirate and biopsy were done, both tests will be considered for response assessment:

- In case of only one assessment with non-missing values: Data of the non-missing test result will be used.
- In case of both assessments with differing, non-missing data: For blast counts, the highest value will be considered. For Auer rods, the positive finding will be considered, if applicable

#### 7.2.1.4.3 Physical examination for Extramedullary disease and/or organomegaly

Extramedullary involvement (CNS and/or soft tissue) is to be assessed at each visit for response assessment. Presence with specification of location or absence of extramedullary disease is to be captured in the eCRF. Extramedullary disease is to be assessed via clinical examination or relevant imaging techniques as clinically appropriate.

In case of extramedullary disease at baseline or (re-)appearance during the study, the lesions need be confirmed cytologically if technically and/or clinically feasible. A clinical assessment will be made in case a cytological confirmation is not possible.

The presence of organomegaly (hepatomegaly and/or splenomegaly) is to be assessed at baseline at visits as part of the response assessment. The modality used: scan or palpation is to be noted.

#### 7.2.1.4.4 Assessments of chromosomal abnormalities

Information on the patient's chromosomal abnormalities/karyotyping based on documented history prior to study entry must be present in his/her source documents. Additional testing to confirm these response categories will not be required and should be done at the discretion of the attending physician.

#### 7.2.1.4.5 Evaluation of transfusion dependency

Transfusion dependency will be assessed at screening as well as during the course of the trial for all patients. Transfusion of blood products will be recorded in a separate module of the eCRF. The type and reason for transfusion, start and end date as well as the number of units will be captured at each visit with hematologic assessment.

A period of one week without any transfusion has been taken as a convention to define the status of transfusion independence to assess response. Any sample of peripheral blood which was taken within seven days after a transfusion will be considered as transfusion dependent.

For the definition of transfusion dependency, it does not matter which type of blood product was transfused. Moreover, the rules and time windows defined below apply not only to blood transfusions but also to erythropoietin, thrombopoietic agents and/or myeloid growth factors.

### 7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, weight, performance status evaluation, ECG, cardiac imaging, laboratory evaluations as well as collecting all serious and non-serious Adverse Events (AE). For details on AE collection and reporting, please refer to Section 8.1.

Clinically 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 and meet the definition of an AE must be recorded on the Adverse Event page of the patient's eCRF.

#### 7.2.2.1 Physical examination

A complete physical examination will be performed at screening at Day 1 of each cycle and at the EOT visit. Visit windows of ± 4 days are allowed (except at cycle 1 Day 1). As specified in Table 7-1, a screening physical examination performed within 4 days of first dosing does not need to be repeated at Cycle 1 Day 1.

The physical examination comprises a total body examination that should include: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the study site.

#### 7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) will be monitored at screening, EOT, and before administration of ceritinib at Day 1 of each cycle. Screening vital sign assessments performed within 4 days of first dosing do not need to be repeated at Cycle 1 Day 1. Vital signs will be measured according to normal medical practice.

#### 7.2.2.3 Height and weight

Height and body weight will be measured. Weight will be measured at the screening visit, at Day 1 of each cycle, and at EOT. Screening weight assessment performed within 4 days of first dosing does not need to be repeated at Cycle 1 Day 1. Height will be collected at screening only.

#### 7.2.2.4 Eastern Cooperative Oncology Group (ECOG) Performance status

The performance status will be assessed according to the ECOG performance status scale (Oken 1982). ECOG performance status will be assessed at screening, at Day 1 of each cycle and at the EOT visit (Appendix M). ECOG performance assessment performed within 4 days of first dosing does not need to be repeated at Cycle 1 Day 1.

#### 7.2.2.5 Laboratory evaluations

Clinical laboratory analyses (hematology, biochemistry, coagulation, lipase, urinalysis, pregnancy test) are to be performed by the local laboratory according to the Visit Schedule outlined in Table 7-1. Visit windows of ± 4 days are allowed (except at cycle 1 Day 1). As

specified in Table 7-1, screening laboratory assessments performed within 4 days of first dosing do not need to be repeated at Cycle 1 Day 1.

Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

More frequent laboratory examinations may be performed at the investigator's discretion if clinically indicated.

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (*e.g.*, require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the Adverse Events eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (CTCAE) version 4.0.3. Additional analyses are left to the discretion of the investigator.

#### 7.2.2.5.1 Hematology

Hematology tests are to be performed by the local laboratory at screening, Day 1 and Day 15 of Cycles 1 and 2, at Day 1 of each subsequent cycle and at EOT according to the Visit Schedule outlined in Table 7-1. The hematology panel includes hemoglobin, hematocrit, platelet count, total red blood cells (RBC), total white blood cells (WBC) count, and a WBC differential including neutrophils, lymphocytes, monocytes, eosinophils and basophils.

#### 7.2.2.5.2 Biochemistry

Biochemistry tests are to be performed by the local laboratory at screening, Day 1 and Day 15 of Cycles 1 and 2, at Day 1 of each subsequent cycle and at EOT according to the Visit Schedule outlined in Table 7-1. The full biochemistry panel includes creatine phosphokinase (CPK) (if total CPK is elevated ≥ CTCAE Grade 2, then weekly measure isoenzymes in blood, and myoglobin in blood and urine until resolved to ≤ CTCAE Grade 1), urea or blood urea nitrogen (BUN), creatinine, uric acid, sodium, magnesium, potassium, glucose, calcium, LDH, total protein, albumin, bicarbonate, phosphorus amylase, lipase, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides. Additionally liver function test including AST/SGOT, ALT/SGPT, GGT, alkaline phosphatase, total, direct and indirect bilirubin will be measured.

#### 7.2.2.5.3 Thyroid function

Thyroid function tests parameters include: thyroid stimulating hormone (TSH), free T3, and free T4.

Thyroid function should be assessed at screening, Day 1 of Cycle 1, Day 1 of Cycle 3, every 3 cycles from C3D1 during the treatment phase (or if clinically indicated), and at EOT.

#### 7.2.2.5.4 Coagulation

International normalized ratio (INR) and pro-thrombin time (PT), activated partial thromboplastin time and fibrinogen will be measured at screening, Day 1 of Cycle 1, and during the treatment phase if clinically indicated.

#### 7.2.2.5.5 Urinalysis

Urinalysis includes dipstick analysis of pH, bilirubin, ketones, leukocytes, protein, glucose, blood, and specific gravity, and will be performed at screening, Day 1 of each cycle and at EOT.

If clinically indicated based on macroscopic urinalysis results, a microscopic evaluation examination will be performed and will include Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, and Epithelial cells.

If screening urinalysis results are $\geq +1$ for protein on dipstick reading, then total urinary protein must be $\leq 500$ mg and measured creatinine clearance must be $\geq 50$ mL/min/1.73m$^2$ in order for the patient to be eligible to participate in the study.

#### 7.2.2.5.6 Pregnancy and assessments of fertility

Women of childbearing potential must undergo a serum pregnancy test at screening to confirm eligibility in the trial ($\leq 4$ days before first dose of study drug), and at EOT. Women of child-bearing potential must additionally undergo a monthly urine pregnancy test during the treatment phase.

In case of pregnancy, the patient must permanently stop study treatment immediately, withdraw from the trial, and the pregnancy must be reported on the Clinical Trial Pregnancy Form.

### 7.2.2.6 Radiological examinations (for safety)

Not applicable.

### 7.2.2.7 Cardiac assessments

#### 7.2.2.7.1 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at screening, Day 1 of Cycles 1 and 2, at Day 1 of every other cycle and at EOT according to the Visit Schedule outlined in Table 7-1.

The interpretation of the tracing must be made by a qualified physician and documented in the ECG section of the eCRF. Each ECG tracing should be labeled with the study number, patient initials (if permitted by local regulations), Patient Number, date, and kept in the source documents at the study site. Only clinically significant abnormalities should be reported in the Adverse Events eCRF. 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 the Novartis Medical Monitor 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.

#### 7.2.2.7.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

MUGA (multiple gated acquisitions) scan or echocardiogram (ECHO) will be used to assess LVEF at screening and during the treatment phase as clinically indicated to assess signs or symptoms of cardiotoxicity. In case of clinically significant abnormalities, they should be reported on the Adverse Events eCRF.

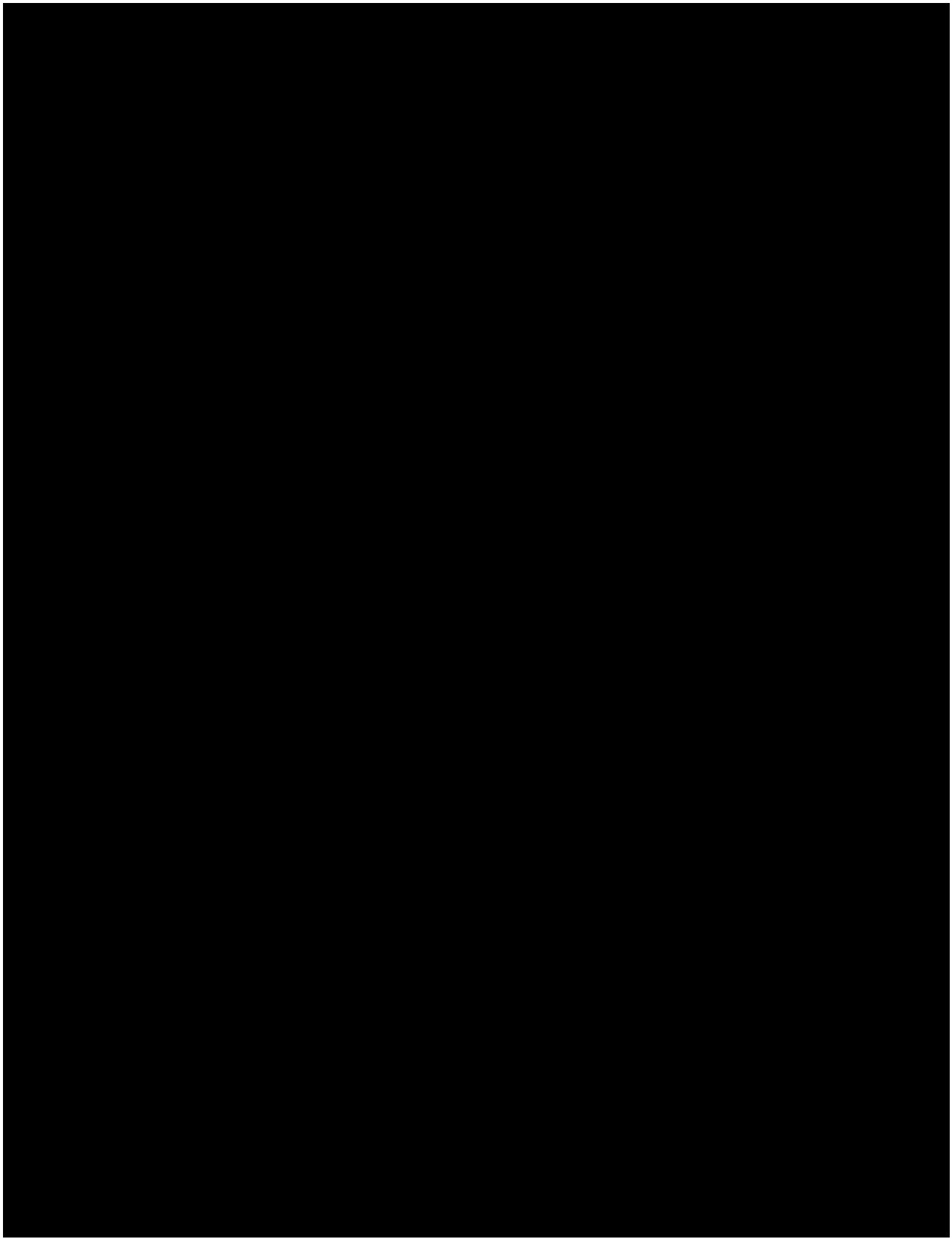
In case a patient develops left ventricular systolic dysfunction while on study treatment dose adjustment guidelines described in Section 6.3 must be followed.

#### 7.2.2.7.3 Cardiac enzymes

Cardiac enzymes (Cardiac troponin-I or troponin-T) will be measured at screening and during the treatment phase if clinically indicated, especially in case of LVEF decrease.

### 7.2.3 Pharmacokinetics

Not Applicable.



### 7.2.5 Other assessments

No additional tests will be performed on patients entered into this study.

# 8 Safety monitoring and reporting

## 8.1 Adverse events

### 8.1.1 Definitions and reporting

An adverse event (AE) 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 who sign the ICF, all AEs will be captured in the AE eCRF from time of signature through 30 days after permanent study treatment discontinuation. For patients who fail the screening, only SAEs will be captured in the AE eCRF page.

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 eCRF. Adverse event monitoring should be continued for at least 30 days 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. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

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:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
   or
   Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.3

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

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

### 8.1.2 Laboratory test abnormalities

#### 8.1.2.1 Definitions and reporting

Laboratory abnormalities will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. 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 eCRF. 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 CTCAEv4.03 does not automatically indicate an 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 and is still, by definition, an adverse event.

## 8.2 Adverse events of special interest

Adverse events of special interest to be monitored for ceritinib have also been identified and include: hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia, gastrointestinal toxicity (nausea, vomiting and diarrhea), and pancreatitis (including lipase and amylase elevations). Details regarding these adverse events are provided in the [Investigator’s Brochure] for ceritinib. Potential emergent new AEs will be monitored during the course of the study.

## 8.3 Serious adverse events

### 8.3.1 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 (specify what this includes)
  - 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
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - 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

### 8.3.2 Reporting

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

SAE collection starts at time of ICF signature whether the patients is a screen failure or not.

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

Information about all SAEs (either initial or follow up information) is collected and recorded on the Serious Adverse Event Report Form on a paper SAE Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), and complete the SAE Report Form in English.

The SAEs recorded on the paper SAE form should be faxed to [redacted] **within 24 hours of awareness of the SAE** to the local Novartis Drug Safety and Epidemiology Department (DS&E). The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Note that any follow up information provided 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. 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.

Refer to Section 7.1.1.2 for additional details regarding the reporting of SAEs which occur during the screening period.

## 8.4 Emergency unblinding of treatment assignment

Not applicable.

## 8.5 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up 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 department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study 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 in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

## 8.6 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's 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.

## 8.7 Data Monitoring Committee

Not applicable.

## 8.8 Steering Committee

Not applicable.

# 9 Data collection and management

## 9.1 Data confidentiality

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

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

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

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

## 9.2 Site monitoring

Before study initiation, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the Investigator or designee will enter all required patient data into the eCRF within 72 hours (3 days) of the patient visit. 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

This study will use Electronic Data Capture (EDC) and the designated investigator staff will enter the data required by the protocol into the eCRF. 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 is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Mutational analysis data will be generated by CLIA certified local labs. We anticipate that the data available in the report will vary from lab to lab. [redacted]

If a tumor sample is obtained at the time of disease progression (optional), data about the sample will be collected in the eCRF.

Laboratory assessments for hematology, biochemistry, coagulation, urinalysis, MUGA and ECGs will be collected locally and entered directly onto the eCRFs.

## 9.4 Database management and quality control

This study will be using eCRFs and the 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 staff 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 current version) terminology.

Data from the screening molecular analysis will be collected locally and entered directly onto the eCRF. [redacted]

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After this action has been completed and the data has been verified to be complete and accurate, the database will be declared locked and the data made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the US Oncology Medical Affairs Franchise Head and the US Oncology Medical Affairs Franchise Vice President.

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

# 10 Statistical methods and data analysis

All data except the primary efficacy variable clinical benefit rate will be analyzed by a designated CRO in collaboration with Novartis. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. The data from all centers that participate in this study will be combined in the final safety and efficacy analysis.

## 10.1 Analysis sets

### 10.1.1 Full Analysis Set

The Full Analysis Set (FAS) will include all patients who have received at least one dose of study drug.

FAS will be used for the analysis of efficacy endpoints.

### 10.1.2 Safety Set

The Safety Set will include all patients who received at least one dose of study treatment and had at least one post-baseline safety assessment.

Please note: the statement that a patient had no adverse event (on the Adverse Event eCRF) constitutes a safety assessment.

## 10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be listed and summarized by patients groups formed by the type of cancer at study entry using the FAS (See Appendix Q for predicted target cancer population). Additional groups may be added based on enrollment (See Appendix Q). Categorical data, such as gender, race, etc., will be presented by frequencies and percentages. Descriptive summary statistics (e.g., frequency, mean, median, range and standard deviation) will be used to present numeric data.

## 10.3 Treatments (study treatment, concomitant therapies, compliance)

### 10.3.1 Study medication

Duration of study treatment exposure, cumulative dose and dose intensity will be summarized by the patient groups as above using the Safety Set. The number of patients with dose changes/interruptions will be presented along with reasons for the dose change/interruption. The safety set will be used for the tables and listings.

### 10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies taken concurrently with the study drugs will be listed and summarized for the FAS by Anatomical Therapeutic Chemical Classification System (ATC) term, preferred term and treatment arm by means of frequency counts and percentages. These summaries will include medications starting on or after the

start of study treatment (defined as cycle 1 day 1) or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed. The safety set will be used for all above mentioned concomitant medication tables and listings.

## 10.4 Primary objective

The primary objective is to assess clinical benefit associated with ceritinib treatment based on local investigator assessment.

For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR or PR or SD ≥ 16 weeks. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices.

For solid tumors, an assessment of CR or PR using RECIST 1.1 must be confirmed at least 4 weeks after initial observation, If the two assessments differ, the best response will be determined by Table 14-5 of Appendix A.

### 10.4.1 Variable

The primary efficacy variable is the clinical benefit rate (CBR) (e.g. defined as CR or PR or SD ≥ 16 weeks for solid tumors).

### 10.4.2 Statistical hypothesis, model, and method of analysis

The study will enroll patients from at least 6 histologic groups. In addition, another group simply referred to as "Other" may be identified and enrolled throughout the study.

We let $Y_i$ be the response indicator for the $i^{th}$ subject, and let $R_g$ be the assumed probability of response within a control population and $\pi_g = \Pr(Y_i = 1 \mid g_i = g)$ be the underlying probability of response for group $g$ within the treatment group. We transform to the logit scale for modeling purposes. Let $\theta_g$ be the mean log odds treatment effect, i.e.:

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right).$$

Thus, $\theta_g$ is the group specific logistic regression coefficient for the treatment within group g. The primary analysis is a set of group specific tests that $\theta_g > 0$, meaning that the treatment is better than the assumed control rate within that group. Thus, we wish to test the set of hypotheses

$$H0g : \theta g \leq 0$$

$$H1g : \theta g > 0$$

We proceed in a Bayesian fashion, assigning a prior distribution (details in Appendix Q) and computing the posterior probability of $H_{1g}$ within each group g. If, at the final analysis,

$$\Pr(\theta_g > 0 \mid \text{data}) > 0.90$$

Then group g will be declared a success (thus, the final analysis produces a separate decision for each group). The trial also allows for early stopping of groups, described below.

The statistical design borrows information across groups with a hierarchical model. The hierarchical model allows dynamic borrowing of information between groups such that more borrowing occurs when the groups are consistent and less borrowing occurs when the groups differ. In this way, the model is a compromise between the two alternate extremes of either a completely pooled analysis or a separate analysis in each group.

The purpose of such an analysis (discussed in more detail in the Appendix Q) is to produce higher power or lower type I error in situations where we see some commonality (identical effects are not required) among the groups. Details of the hierarchical model is provided in Appendix Q.

### 10.4.3 Evaluation of trial success and futility

The clinical benefit rate will be evaluated for futility and early success by comparing posterior quantities for the rate to pre-specified early stopping criteria. The evaluations are planned to occur after the first 30 patients are dosed for at least 16 weeks or discontinued, then every 13 weeks thereafter until the enrollment closure of the study. An additional CBR evaluation will be performed after the database lock for the primary CSR.

#### Early Futility

If there is less than 10% probability that the response rate in a group exceeds the historical rate $R_g$, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$\Pr(\pi_g > R_g) < 0.10.$$

A group is only eligible for early stopping once a minimum of 10 patients has been evaluated for response in that group.

#### Early Success

If there is at least 95% probability that the response rate in a group exceeds the historical rate, then the group will stop enrollment early for success. Formally, enrollment will stop early for success if:

$$\Pr(\pi_g > R_g) > 0.95.$$

A minimum of 15 subjects will need to be evaluated prior to declaring a group to be efficacious.

#### Final Analysis

The final analysis will occur when both accrual and follow-up are complete in all groups. If, at the completion of the trial, there is at least 90% probability that the response rate in a group exceeds the historical rate, then the group will be considered a success. Formally if:

$$\Pr(\pi_g > R_g) > 0.90.$$

In addition, a group will be considered as "promising' if:

$$0.80< Pr(\pi_g > R_g) < 0.90.$$

### 10.4.4 Handling of missing values/censoring/discontinuations

A patient who has not progressed or died at the date of the analysis cut-off would have his/her PFS and OS censored at the time of the last adequate assessment before the cut-off date. Any disease assessment indicating response status other than "unknown" or "not done" is considered an adequate response assessment.

### 10.4.5 Supportive analyses

Not applicable.

## 10.5 Secondary objectives

### 10.5.1 Key secondary objective(s)

The key secondary objective of this study is to assess Overall Response (OR) of Partial Response (PR) or Complete Response (CR) based on local investigator assessment.

For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices.

The overall response rate (PR plus CR) and its 95% exact confidence interval will be provided for each patient group. In the event where sample size in each patient group is small (<10), only ORR summary for the entire study cohort will be presented.

### 10.5.2 Other secondary efficacy objectives

The secondary objectives of the study:

- To assess progression free survival (PFS) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria
- To assess overall survival
- To assess duration of response (DOR) based on local investigator assessment per RECIST 1.1 or other appropriate hematological response criteria
- To assess safety and tolerability

The secondary efficacy variable progression free survival (PFS) is defined as the time from the date of first dose to the date of first documented disease progression or relapse or death due to any cause.

PFS will be summarized and graphed using the Kaplan-Meier product-limit method for the entire study cohort. For cohorts with at least 10 subjects, separate PFS analyses will be conducted for each cohort. Patients who drop-out without progression will be censored at the time of last adequate assessment. The estimates of the $25^{th}$, median, $75^{th}$ percentiles of the PFS and their 95% confidence intervals will be provided, if applicable.

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

OS will be summarized and graphed using the product-limit method as above.

The duration of response applies only to patients whose best response was PR or CR. For patients with solid tumors the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR. For hematologic tumors other appropriate hematological response criteria will apply and are included in the appendices. The duration of response is defined as the time from the first documented response to the date first documented disease progression or relapse or death due to any cause. The duration of response will be summarized descriptively for the entire study cohort.

If the study primary efficacy endpoint is not met, Novartis may decide not to conduct some of the above secondary efficacy analyses but instead provide those endpoints in listings only.

### 10.5.3 Safety objectives

For all safety analyses, the safety set will be used. All listings and tables will be presented by patient groups.

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs) will be considered as appropriate. All safety data will be listed.

The safety summary tables will include only assessments collected no later than 30 days after study treatment discontinuation. Those collected later than 30 days after study treatment discontinuation will be flagged in listings.

#### 10.5.3.1 Analysis set and grouping for the analyses

##### 10.5.3.1.1 Adverse events (AEs)

All adverse events recorded during the study will be summarized. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, maximum severity (based on CTCAE v4.03), type of adverse event, relationship to the study treatment by treatment group. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and patient group.

Adverse events will be summarized by presenting the number and percentage of patients by system organ class and/or preferred term, the maximum severity (based on CTCAE v4.03) and treatment arm. Adverse events related to study treatment will also be summarized. In addition, adverse events of related nature may be analyzed by categories regrouping the relevant preferred terms, as appropriate.

##### 10.5.3.1.2 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade will be calculated using appropriate common terminology criteria (CTCAE v4.03).

A severity grade of 0 will be assigned when the value is within normal limits. For lab parameters for which severity grades are determined both through normal limits and absolute cut-offs, in the unlikely case when a local laboratory normal range overlaps into the higher (i.e. non-zero) CTCAE grade, the laboratory value will still be taken as within normal limits and assigned a CTCAE grade of zero.

A listing of laboratory values will be provided by laboratory parameter, patient, and treatment arm. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities). Lab values collected later than 30 days after study treatment discontinuation will be flagged in the listings.

The following by-group summaries will be generated separately for hematology, and biochemistry parameters:

- 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) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

#### 10.5.3.1.3 Other safety data

Summary statistics for data from other tests will be provided, notable values will be flagged, and any other information collected will be listed as appropriate.

Descriptive summary statistics will be provided for :

- Electrocardiograms: changes from baseline to last available ECG results
- Cardiac imaging: number and percentage of patients with notable LVEF values
- Vital signs: number and percentage of patients with at least one post-baseline vital sign abnormality
- ECOG performance status: shift table comparing baseline to worst post baseline ECOG performance status.
- All other safety related procedures as required
- Listings with flagged notable values and any other information collected will be provided as appropriate.

## 10.7 Interim analysis

There is no plan for a formal interim analysis of safety or other secondary endpoints for this study. However, for publication or other purposes, interim data review of clean data will be performed as necessary. At these interim reviews, patient demographics/baseline characteristics, the primary and secondary endpoints as applicable, and all important safety endpoints will be summarized.

No formal report will be issued for these interim data reviews.

## 10.8 Sample size calculation

The sample size was chosen by the usual criteria of obtaining adequate power for the alternative hypothesis of interest as shown in Table 14-18 of Appendix Q. This hypothesis corresponds to a generally effective treatment across groups and incorporates variation in treatment effects to reflect the realistic expectation that treatment effects may differ by group. In this setting, analytical power calculations are not possible, but the design was simulated to obtain the power of the study as shown in the appendix. The sample sizes shown (minimum of 10 for futility stopping, minimum of 15 for early success and maximum of 30 as a group cap) achieve adequate power for the alternative hypothesis. The simulations included the expected variable accrual by simulating a Poisson process with expected accrual also shown in the appendix.

# 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 International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), 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. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

## 11.3 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 investigators in a separate document with a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH and 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 approval.

Women of child bearing potential and fertile males 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. Women of child bearing potential must agree to adhere to contraception requirement until at least 3 months after the final dose of study treatment. Fertile males must agree to adhere to contraception requirement until at least 3 months after the final dose of study treatment. If there is any question that the patient will not reliably comply, they should not be entered in the study.

## 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 4.3.

## 11.5 Publication of study protocol and results

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

## 11.6 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 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. An audit trail will be maintained by the system.

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 is 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 clinical study report (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/REB at the study site should be informed within 10 working days.

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LDK378 Investigator’s Brochure ed.6.

# 14 Appendices

## 14.1 Appendix A: Criteria for therapeutic response/outcome assessment of solid tumors and/or lymph nodes (based on RECIST 1.1)

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

### 14.1.1 Measurability of tumor lesions at baseline

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

#### 14.1.1.1 Measurable

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

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

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

#### 14.1.1.2 Non-measurable

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

##### 14.1.1.2.1 Bone lesions

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

#### 14.1.1.2.2 Cystic lesions

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

#### 14.1.1.2.3 Lesions previously treated

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

### 14.1.2 Specification by methods of measurement

#### 14.1.2.1 Measurement of lesions

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

#### 14.1.2.1.1 Target lesions

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

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

#### 14.1.2.1.2 Non-target lesions

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

#### 14.1.2.2 Response criteria

#### 14.1.2.2.1 Evaluation of target lesions

This section provides the definitions of the criteria used to determine overall tumor response for target lesions as shown below in Table 14-1.

**Table 14-1 Evaluation of target lesions**

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

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

#### 14.1.2.2.2 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions as shown below in Table 14-2. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

**Table 14-2 Evaluation of non-target lesions**

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

#### 14.1.2.2.3 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which **was not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as

a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment.

- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥10 mm for the first time in the study plus 5 mm absolute increase.
  a. Negative FDG-PET at baseline, with a positive[1] FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

### 14.1.3 Evaluation of best overall response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as indicated below in Table 14-3 and Table 14-4.

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence. The best overall response for CR and PR will be determined at 8 weeks as indicated below in Table 14-5.

**Table 14-3 Time point response: patients with target (+/- non-target) disease**

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

**Table 14-4 Time point response: patients with non-target disease only**

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

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

**Table 14-5 Best overall response when confirmation of CR and PR required**

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

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

### 14.1.4 References (available upon request)

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## 14.2 Appendix B: Criteria for therapeutic response/outcome assessment in lymphoma studies (based on Cheson response criteria)

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

### 14.2.1 Definitions and criteria for normalization

#### 14.2.1.1 Definitions

##### 14.2.1.1.1 Nodal vs extranodal lesion

A lesion is categorized based on the location as:

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

### 14.2.2 Measurability of Tumor Lesions at Baseline

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

#### 14.2.2.1 Measurable Nodal and extranodal lesions

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

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

Patients should have at least one measurable nodal lesion greater than 20 mm in the long axis.

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

#### 14.2.2.2 Classification of lymph nodes

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

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

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

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

#### 14.2.2.3 Criteria for normalization of lesions

The normalization of lesions is defined as follow:

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

### 14.2.3 Specification by methods of measurement

#### 14.2.3.1 Measurement of lesions

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

##### 14.2.3.1.1 PET

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

##### 14.2.3.1.2 CT scan (or MRI)

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

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

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

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

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

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

#### 14.2.3.1.3 Bone marrow assessment

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

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

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

#### 14.2.3.1.4 Physical examination and assessment of B-symptoms

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

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

B-symptoms are defined as follows:

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

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

### 14.2.4 Evaluation of Radiological Response

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

Definitions of Response for Lymphoma patients are listed in Table 14-6. To evaluate disease response to treatment, all index and non-index lesions will be followed and assessed throughout the study. At each assessment, response is evaluated separately for the **index lesions** (Table 14-9) and **non-index lesions** (Table 14-8) identified at Screening, then a combined overall radiological response is determined (Table 14-11).

**Table 14-6 Response Definition for Lymphoma**

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

#### 14.2.4.1 Evaluation of Index Lesions (nodal and extranodal)

##### 14.2.4.1.1 When index nodal lesions are not in complete response

The response for index lesions is evaluated by calculating the Sum of the Products of Diameters (SPD) of all index lesions (see Table 14-7), except when there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions) (see Section 14.2.4.1.2).

**Table 14-7 Radiological status based on SPD calculation for all index lesions**

| Response Criteria[1] | Evaluation of index lesions |
|---|---|
| Complete Response (CR) | See Table 14-9 below (not based on SPD calculation for all index lesions) |
| Partial Response (PR) | At least 50% decrease from Screening in the SPD of all index lesions |
| Stable Disease (SD) | Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD |
| Progressive Disease (PD) | At least a 50% increase from nadir[2] in the SPD of all index lesions |

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

##### 14.2.4.1.2 When index nodal lesions are in complete response

When there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions as defined in Section 14.2.4.2: all index lesion ≤ 15 mm in long axis), the SPD for these index nodal lesions may not be equal to zero and therefore a calculation of a SPD for all index lesions may be misleading. Therefore, by default, a specific response for extranodal index lesions needs to be evaluated, based on the SPD calculation restricted to all index extranodal lesions only (see Table 14-8).

**Table 14-8 Radiological response criteria for index extranodal lesions in case of CR in index nodal lesions**

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

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

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

#### 14.2.4.1.3 Evaluation of response for all index lesions

The evaluation of response for all index lesions is based on the combination of the response for index nodal lesions (CR or non-CR), the response for index extranodal and the status based on the SPD calculated on all index lesions (nodal and extranodal), as described in Table 14-9.

**Table 14-9 Radiological response for index lesions**

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

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

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

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

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

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

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

Then, this status for each non-index lesion (or group of non-index lesions) will lead to a global response for non-index lesions (Table 14-10):

**Table 14-10 Response criteria for non-index lesions (nodal, splenic and/or hepatic nodules and other extranodal lesions)**

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

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

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

#### 14.2.4.2 New lesions

The appearance of

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

OR

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

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

##### 14.2.4.2.1 Overall radiological response

Overall radiological response is calculated as shown in Table 14-11.

**Table 14-11 Overall radiological response at each assessment**

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

| Index lesions | Non-index lesions[1] | New lesions | Overall radiological response |
|---|---|---|---|

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

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

#### 14.2.4.2.2 Evaluation of overall disease response

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

#### 14.2.4.2.3 Bone marrow re-assessment at time of radiological CR

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

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

#### 14.2.4.2.4 Overall disease response

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

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

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

For patients whose radiological response is anything other than CR, assessment of bone marrow, liver, spleen and B-symptoms will not be required in evaluating overall response and

overall disease response is the same as radiological response. However any new or recurrent bone marrow involvement at any time during follow-up will be considered PD.

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

### 14.2.5 References (available upon request)

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

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

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

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

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

## 14.3 Appendix C: Ann Arbor staging classification

| Stage | Area of involvement |
|---|---|
| I | Single lymph node group |
| II | Multiple lymph node groups on the same side of the diaphragm |
| III | Multiple lymph node groups on both sides of the diaphragm |
| IV | Multiple extranodal sites or lymph nodes and extranodal disease |
| X | Bulk disease > 10 cm |
| E | Extranodal extension or single isolated site of extranodal disease |
| Class A are patients who experience no B symptoms | |
| Class B are patients experience unexplained fever of ≥ 38°C; unexplained, recurrent drenching night sweats; or unexplained loss of >10% body weight within the previous 6 months | |

[1] Cotswolds modification of Ann Arbor staging system adapted from 2007 NCCI guidelines for non-Hodgkin's lymphoma

## 14.4 Appendix D: Rai Staging System[a]

| Stage | Area of involvement | Risk Status |
|---|---|---|
| 0 | Lymphocytosis, lymphocytes in blood >15 x $10^9$/L and >40% lymphocytes in bone marrow | Low |
| I | Stage 0 with enlarged node(s) | Intermediate |
| II | Stage 0-1 with splenomegaly, hepatomegaly, or both | Intermediate |
| III[b] | Stage 0-II with hemoglobin < 11.0 g/dL or hematocrit <33% | High |
| IV[b] | Stage 0-III with platelets <100 x $10^9$/L | High |

[a] Research originally published in Blood. Rai KR et al. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46(2):219-234. (c) The American Society of Hematology
[b] Immune-mediated cytopenias are not the basis for these stage definitions.

## 14.5 Appendix E: Criteria for Response assessment in Acute Myeloid Leukemia (based on IWG and Cheson)

Disease assessments will be based on standardized response criteria as defined by the International Working Group (IWG) for AML (Cheson et al 2003).

| **Response classification in AML at a given evaluation time (Cheson 2003)** | |
|---|---|
| **Response category** | **Definition[#]** |
| Complete remission (CR) | **Bone marrow**<br>< 5% blasts<br>no blasts with Auer rods<br><br>**Peripheral blood**<br>neutrophils ≥ 1.0 x $10^9$/L<br>platelets ≥ 100 x $10^9$/L<br>≤ 1% blasts<br>No evidence of extramedullary disease (such as CNS or soft tissue involvement).<br>Transfusion independent (see Section 7.2.1.4.5).<br><br>In case all criteria for CR apply and the patient receives platelet and/or neutrophil transfusions, the patient will be assessed as CRi. |

| Response classification in AML at a given evaluation time (Cheson 2003) | |
|---|---|
| **Response category** | **Definition#** |
| Complete remission with incomplete blood count recovery (CRi) | **Bone marrow**<br>< 5% blasts<br>no blasts with Auer rods<br><br>**Peripheral blood**<br>neutrophils < 1.0 x $10^9$/L and/or platelets < 100 x $10^9$/L<br>≤ 1% blasts<br>No evidence of extramedullary disease (such as CNS or soft tissue involvement).<br>Transfusion-independent (see Section 7.2.1.4.5). Exception: Platelet and neutrophil transfusions are allowed. |
| Partial Remission (PR) | **Bone marrow**<br>50% or greater decrease (absolute range 5-25% blasts)<br>< 5% of blasts contain Auer rods<br><br>**Peripheral blood**<br>neutrophils < 1.0 x $10^9$/L and/or platelets < 100 x $10^9$/L<br><br>No evidence of extramedullary disease (such as CNS or soft tissue involvement). |
| Treatment failure | Treatment failure includes those patients for whom treatment has failed to achieve PR, CRi or CR throughout the treatment. |
| Relapse from CR or CRi* | Only in patients with a CR or CRi:<br>Reappearance of blasts in peripheral blood (> 1%) OR<br>≥ 5% blasts in bone marrow OR<br>(Re-)appearance of extramedullary disease |
| No response | In case a patient does not achieve CR, CRi, PR or relapse for an individual response assessment. |
| Unknown | In case the response assessment was not done, the baseline assessment was not done, the assessment was incomplete or was not done within the respective time frame. |
| # If not defined otherwise, all of the criteria apply.<br>* Cheson et al (2003) does not specify relapse after PR but this may be considered in Phase I or II protocols. | |

**Table 14-12 Exploratory AML response categories according to IWG**

| Response category | Definition |
|---|---|
| Cytogenetic complete remission (CRc) | All criteria for CR plus<br>no cytogenetic abnormalities |
| Molecular complete remission (CRm) | All criteria for CRc plus<br>no leukemic cells by RQ-PCR assay |

## 14.6 Appendix F: Criteria for Response assessment in Acute Lymphoblastic Leukemia (based on NCCN Guidelines Version 1.2013)

| Response classification in ALL for Blood and Bone Marrow at a given evaluation time | |
|---|---|
| **Response category** | **Definition#** |
| Complete remission (CR) | No circulating blasts or extramedullary disease (such as lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, CNS or soft tissue involvement)<br>Trilineage hematopoiesis (TLH) and < 5% blasts<br>neutrophils ≥ 1.0 x $10^9$/L<br>platelets ≥ 100 x $10^9$/L<br>No recurrence for 4 weeks |

| **Response classification in ALL for Blood and Bone Marrow at a given evaluation time** | |
|---|---|
| **Response category** | **Definition#** |
| Complete remission with incomplete blood count recovery (CRi) | **Peripheral blood**<br>Recovery of platelets but < 100 x $10^9$/L or neutrophils is < 1.0 x $10^9$/L. |
| Progressive Disease (PD) | Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease. |
| Treatment failure | Treatment failure includes those patients for whom treatment has failed to achieve a CR at the end of treatment |
| Relapse from CR or CRi* | Only in patients with a CR or CRi:<br>Reappearance of blasts in peripheral blood (> 1%) OR<br>≥ 5% blasts in bone marrow OR<br>(Re-)appearance of extramedullary disease |
| No response | In case a patient does not achieve CR, CRi, PR or relapse for an individual response assessment. |
| Unknown | In case the response assessment was not done, the baseline assessment was not done, the assessment was incomplete or was not done within the respective time frame. |
| # If not defined otherwise, all of the criteria apply. | |

## 14.7 Appendix G: Criteria for Response assessment in Chronic Myelogenous Leukemia (based on NCCN Guidelines Version 4. 2013)

| **Response classification in CML for hematologic, cytogenetic, and molecular evaluation at a given evaluation time** | |
|---|---|
| **Response category** | **Definition#** |
| Complete hematologic response (CR)[1] | Complete normalization of peripheral blood counts with leukocyte count < 10 x $10^9$/L<br>platelets < 450 x $10^9$/L<br>No immature cells such as myelocytes, promyelocytes, or blasts in peripheral blood<br>No signs and symptoms of disease with disappearance of splenomegaly |
| Cytogenetic response[2,3] | Complete<br>No Ph-positive metaphases<br>Partial<br>1% - 35% Ph-positive metaphases<br>Major<br>0% - 35% Ph-positive metaphases (complete + partial)<br>Minor<br>> 35% Ph-positive metaphases |
| Molecular response[4,5] | Complete<br>No detectable BCR-ABL mRNA by QPCR using an assay with a sensitivity of at least 4.5 logs below standardized baseline.<br>Major<br>≥ 3 log reduction in international scale of BCR-ABL mRNA |
| Treatment failure | Treatment failure includes those patients for whom treatment has failed to achieve a complete hematologic response (CR) throughout treatment. |
| No response | In case a patient does not achieve CR, PR or relapse for an individual response assessment. |
| Unknown | In case the response assessment was not done, the baseline assessment was not done, the assessment was incomplete or was not done within the respective time frame |

| Response classification in CML for hematologic, cytogenetic, and molecular evaluation at a given evaluation time | |
|---|---|
| **Response category** | **Definition#** |
| # If not defined otherwise, all of the criteria apply.<br>[1] Federl S et al: Chronic myelogenous leukemia: Biology and therapy. Ann Intem Med 1999; 131:207-219.<br>[2] A minimum of 20 metaphases should be examined.<br>[3] O'Brien SG, et al: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.<br>[4] Hughes TP, et al: Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnoses chronic myeloid leukemia. N Engl J Med 2003;349:1423-1432<br>[5] Hughes T, et al: Monitoring CML patients responding to treatment with tyrosine kinase inhibitors; review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108:28-37 | |

## 14.8 Appendix H: Criteria for Response assessment in Chronic Lymphocytic Leukemia (based on modified IWG guidelines)

Disease assessments will be based on standardized response criteria as defined by the modified IWG guidelines for CLL. Response in CLL must meet the criteria in both Group A and Group B. Group A criteria defines tumor load. Group B criteria define the function of the hematopoietic system (or marrow).

### Response Definition for Chronic Lymphocytic Leukemia[1]

| **Group A Response for Tumor Burden** | | | |
|---|---|---|---|
| **Response** | **Nodal Masses** | **Organomegaly** | **Bone Marrow** |
| CR | None > 1.5 cm | No splenomegaly<br>No hepatomegally | Normocellular >30% Lymph. No B lymphoid nodules |
| CRi | None > 1.5 cm | No splenomegaly<br>No hepatomegally | Hypocellular marrow |
| PR | Decrease ≥50% | Spleen/Liver decrease ≥50 | 50% reduction in marrow infiltrate, or B-lymphoid nodules |
| **Group B Response for hepatopoietic system[2]** | | | |
| **Response** | **Platelet count** | **Hemoglobin** | **Neutrophils** |
| CR | >100 x $10^9$/L | >11 g/dL | >1.5 x $10^9$/L |
| CRi | If meets criteria from Group A but does not meet criteria from Group B | | |
| PR | >100 x $10^9$/or increase ≥50% over baseline | >11 g/dL or increase ≥50% over baseline | >1.5 x $10^9$/L or >50% improvement over baseline |
| SD | Failure to attain CR/CRi/PR or PD | | |
| Relapsed disease or PD | Appearance of any new lesions; at least one of the above criteria. Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease | | |
| Hallek M, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia updating the National Cancer Institute-Working Group 1996 Guidelines. Blood 2008; 111:5446-5456<br>All values are without transfusion or hepatopoietic growth factors | | | |

## 14.9 Appendix I: Criteria for Response assessment in Myelofibrosis (based on modified IWG-MRT guidelines and European LeukemiaNet (ELN) consensus report)[1]

| Response category | Definition |
|---|---|
| CR | Bone marrow: Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF† and<br>Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥ 1 X $10^9$/L and <UNL;<br>Platelet count ≥100 X $10^9$/L and <UNL; <2% immature myeloid cells‡ and<br>Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH |
| PR | Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 X $10^9$/L and <UNL; platelet count ≥100 X $10^9$/L and <UNL; <2% immature myeloid cells‡ and<br>Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or<br>Bone marrow: Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF†, and peripheral blood: Hemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1 X $10^9$/L and <UNL; platelet count ≥50, but <100 X $10^9$/L and <UNL; <2% immature myeloid cells‡ and<br>Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH |
| Clinical improvement (CI) | The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§ |
| Anemia response | Transfusion-independent patients: a ≥20 g/L increase in hemoglobin level‖<br>Transfusion-dependent patients: becoming transfusion-independent^ |
| Spleen response# | A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable** or<br>A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%**<br>A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response<br>A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction |
| Symptoms response | A ≥50% reduction in the MPN-SAF TSS†† |
| Progressive disease‡‡ | Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or<br>A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or<br>A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or<br>Leukemic transformation confirmed by a bone marrow blast count of ≥20% or<br>A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 X $10^9$/L that lasts for at least 2 weeks |
| Stable disease | Belonging to none of the above listed response categories |
| Relapse | No longer meeting criteria for at least CI after achieving CR, PR, or CI, or<br>Loss of anemia response persisting for at least 1 month or<br>Loss of spleen response persisting for at least 1 month |

| Response category | Definition |
|---|---|
| **Recommendations for assessing treatment-induced cytogenetic and molecular changes** | |
| Cytogenetic remission | At least 10 metaphases must be analyzed for cytogenetic response evaluation and requires confirmation by repeat testing within 6 months window<br>CR: eradication of a preexisting abnormality<br>PR: ≥50% reduction in abnormal metaphases<br>(partial response applies only to patients with at least ten abnormal metaphases at baseline) |
| Molecular remission | Molecular response evaluation must be analyzed in peripheral blood granulocytes and<br>requires confirmation by repeat testing within 6 months window<br>CR: Eradication of a pre-existing abnormality<br>PR: ≥50% decrease in allele burden<br>(partial response applies only to patients with at least 20% mutant allele burden at baseline) |
| Cytogenetic/molecular relapse | Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing |

[1]Tefferi et al. (2013) Revised response criteria for myelofibrosis: International Working (IWG-MRT) and European LeukemiaNet (ELN) consensus report Group-Myeloproliferative Neoplasms Research and Treatment. Blood; 2013 122: 1395-1398

EMH, extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH); LCM, left costal margin; UNL, upper normal limit.

Grading of MF is according to the European classification

Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 2005;90:1128.

It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

‡Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.

§See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25 000 X $10^9$/L and absolute neutrophil count of ≥0.5 X $10^9$/L.

‖Applicable only to patients with baseline hemoglobin of<100 g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment (see as follows), but have received transfusions within the previous month, the pre-transfusion hemoglobin level should be used as the baseline.

^Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive “rolling” 12-week
interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L.

#In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.

**Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

††Symptoms are evaluated by the MPN-SAF TSS.[1] The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

‡‡Progressive disease assignment for splenomegaly requires confirmation my MRI or computed tomography showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to post-treatment measurements.

## 14.10 Appendix J: Criteria for Response assessment in polycythemia vera (based on modified IWG-MRT guidelines and European LeukemiaNet (ELN) consensus report)[1]

| Response categories | Required criteria |
|---|---|
| Complete remission | Durable resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND<br>Durable peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count ≤400 X $10^9$/L, WBC count <10 X $10^9$/L, AND<br>Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND<br>Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of tri-linear hyperplasia, and absence of >grade 1 reticulin fibrosis |
| Partial remission | Durable resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND<br>Durable peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count ≤400 X $10^9$/L, WBC count <10 X $10^9$/L, AND<br>Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND<br>Without bone marrow histological remission defined as persistence of tri-linear hyperplasia. |
| No response | Any response that does not satisfy partial remission |
| Progressive disease | Transformation into post-PV myelofibrosis, myelodysplastic syndrome or acute leukemia‡ |

Molecular response is not required for assignment as complete response or partial response. Molecular response evaluation requires analysis in peripheral blood granulocytes. Complete response is defined as eradication of a preexisting abnormality. Partial response applies only to patients with at least 20% mutant allele burden at baseline. Partial response is defined as ≥ 50% decrease in allele burden.
WBC, white blood cell.
†Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.[2]
‡For the diagnosis of post-PV myelofibrosis, see the IWG-MRT criteria[3]; for the diagnosis of myelodysplastic syndrome and acute leukemia, see WHO criteria.

**References (available upon request)**

[1]Barosi G, et al; Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 2013 121: 4778-4781
[2]Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs [published correction appears in J Clin Oncol. 2012;30(36):4590]. J Clin Oncol. 2012;30(33):4098-4103
[3]Barosi G, Mesa RA, Thiele J, et al; International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). Proposed criteria for the diagnosis of post-polycythemia vera and postessential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia. 2008;22(2):437-438

## 14.11 Appendix K: Criteria for Response assessment in Essential thrombocythemia (based on modified IWG-MRT guidelines and European LeukemiaNet (ELN) consensus report)[1]

| Response category | Definition |
|---|---|
| Complete remission | Durable resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement,† AND<br>Durable peripheral blood count remission, defined as: platelet count ≤400 X $10^9$/L, WBC count <10 X $10^9$/L, absence of leukoerythroblastosis, AND<br>Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND<br>Bone marrow histological remission defined as disappearance of megakaryocyte hyperplasia and absence of >grade 1 reticulin fibrosis. |
| Partial remission | Durable resolution of disease-related signs including palpable hepatosplenomegaly, and large symptoms improvement, AND<br>Durable peripheral blood count remission, defined as: platelet count ≤400 X $10^9$/L, WBC count <10 X $10^9$/L, absence of leukoerythroblastosis, AND<br>Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND<br>Without bone marrow histological remission, defined as the persistence of megakaryocyte hyperplasia. |
| No response | Any response that does not satisfy partial remission |
| Progressive disease | Transformation into PV, post-ET myelofibrosis, myelodysplastic syndrome or acute leukemia‡ |

Molecular response is not required for assignment as complete response or partial response. Molecular response evaluation requires analysis in peripheral blood granulocytes. Complete response is defined as eradication of a preexisting abnormality. Partial response applies only to patients with at least 20% mutant allele burden at baseline. Partial response is defined as ≥50% decrease in allele burden.
WBC, white blood cell.
†Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.[3]
‡For the diagnosis of PV see World Health Organization criteria (WHO)[4]; for the diagnosis of post-ET myelofibrosis, see the IWG-MRT criteria[2]; for the diagnosis of myelodysplastic syndrome and acute leukemia, see WHO criteria.[4]

**References (available upon request)**

[1] Barosi G, et al; Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 2013 121: 4778-4781
[2] Barosi G, Mesa RA, Thiele J, et al; International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). Proposed criteria for the diagnosis of post-polycythemia vera and postessential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia. 2008;22(2):437-438.
[3] Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs [published correction appears in J Clin Oncol. 2012;30(36):4590]. *J Clin Oncol*. 2012;30(33):4098-4103.
[4] Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2008.

## 14.12 Appendix L: Criteria for Response assessment in Myelodysplasia (based on modified IWG guidelines)[1]

| Category | Response Criteria |
|---|---|
| Complete remission | Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines*<br>Persistent dysplasia will be noted*<br>Peripheral blood<br>● Hgb ≥ 11 g/dL<br>● Platelets ≥ 100 x $10^9$/L<br>● Neutrophils ≥ 1.0 x $10^9$/L<br>● Blasts 0% |
| Partial remission | All CR criteria if abnormal before treatment except:<br>Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%<br>Cellularity and morphology not relevant |
| Marrow CR | Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment<br>Peripheral blood: if HI responses, they will be noted in addition to marrow CR |
| Stable disease | Failure to achieve at least PR, but no evidence of progression for > 8 wks |
| Failure | Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment |
| Relapse after CR or PR | At least 1 of the following:<br>● Return to pretreatment bone marrow blast percentage<br>● Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets<br>● Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence |
| Cytogenetic response | Complete - Disappearance of the chromosomal abnormality without appearance of new ones<br>Partial - At least 50% reduction of the chromosomal abnormality |
| Disease progression | For patients with:<br>● Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts<br>● 5%-10% blasts: ≥ 50% increase to > 10% blasts<br>● 10%-20% blasts: ≥ 50% increase to > 20% blasts<br>● 20%-30% blasts: ≥ 50% increase to > 30% blasts<br>Any of the following:<br>● At least 50% decrement from maximum remission/response in granulocytes or platelets<br>● Reduction in Hgb by > 2 g/dL<br>● Transfusion dependence |
| *Dysplastic changes should consider the normal range of dysplastic changes (modification). | |
| [1]Cheson, et al. Clinical application and proposal for modification of the InternationalWorking Group (IWG) response criteria in myelodysplasia. blood-2005-10-4149. | |

## 14.13 Appendix M: Eastern Cooperative Oncology Group Performance Status

| 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.<br>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 |

## 14.14 Appendix N: International Myeloma Working Group (IMWG) uniform response criteria for multiple myeloma

| Response | IMWG Criteria |
|---|---|
| sCR | CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4] |
| CR | Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3] |
| VGPR | Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-component plus urine M-component < 100 mg per 24 hr |
| PR | > 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >90% or to < 200 mg/24 h<br>If the serum and urine M-protein are unmeasurable,[5] a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria<br>If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30%<br>In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required |
| SD | Not meeting criteria for CR, VGPR, PR, or progressive disease |
| PD[5] | Increase of > 25% from lowest response value in any one or more of the following:<br>Serum M-component and/or (the absolute increase must be > 0.5 g/dL)[6]<br>Urine M-component and/or (the absolute increase must be > 200 mg/24 h)<br>Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL<br>Bone marrow plasma cell percentage; the absolute percentage must be > 10%[7]<br>Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas<br>Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder |
| Relapse | Clinical relapse requires one or more of:<br>Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[6] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice<br>Development of new soft tissue plasmacytomas or bone lesions<br>Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion<br>Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L]<br>Decrease in haemoglobin of > 2 g/dL [1.25 mmol/L]<br>Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more] |

| Response | IMWG Criteria |
|---|---|

[1] BGM Durie et al. International uniform response criteria for multiple myeloma. Leukemia (2006) 1-7.
[2] Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9
Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.
[3] Confirmation with repeat bone marrow biopsy not needed.
[4] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.
[5] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.
[6] For progressive disease, serum M-component increases of >1 gm/dL are sufficient to define relapse if starting M-component is >5 g/dL.
[7] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.
[8] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

## 14.15 Appendix O: Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

Name: _____ Date: _____

Fill out the form below to track the burden of your symptoms.

For each symptom, please **circle the number** that best describes how severe that symptom is, on a scale of 0 to 10, with **0 being absent or as good as it can be** and **10 being worst imaginable**. Make sure you circle a number for every symptom. Be sure to **share your answers** with your haematologist or other healthcare professional.

### Symptom - 1 to 10, 0 if absent and 10 being worst imaginable

Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past ***24 hours***

Fatigue

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| (ABSENT) | | | | | | | | | | (WORST IMAGINABLE) |

Circle the one number that describes how much difficulty you have had with each of the following symptoms during the ***past week***

Filling up quickly when you eat (early satiety)

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| (ABSENT) | | | | | | | | | | (WORST IMAGINABLE) |

Abdominal discomfort

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| (ABSENT) | | | | | | | | | | (WORST IMAGINABLE) |

| Inactivity | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| (ABSENT) | | | | | | | | | | (WORST IMAGINABLE) |

| Problems with concentration - compared to before my diagnosis | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| (ABSENT) | | | | | | | | | | (WORST IMAGINABLE) |

| Night sweats | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| (ABSENT) | | | | | | | | | | (WORST IMAGINABLE) |

| Itching (pruritus) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| (ABSENT) | | | | | | | | | | (WORST IMAGINABLE) |

| Bone pain (diffuse, not joint pain or arthritis) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| (ABSENT) | | | | | | | | | | (WORST IMAGINABLE) |

| Fever (> 37.8°C or 100°F) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| (ABSENT) | | | | | | | | | | (WORST IMAGINABLE) |

| Unintentional weight loss last 6 months | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| (ABSENT) | | | | | | | | | | (WORST IMAGINABLE) |

To help you get a clear overall picture of how you are feeling, you can add up all your scores to calculate your Total Symptom Score. Total:

[1]Adapted from Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs [published correction appears in J Clin Oncol. 2012;30(36):4590]. J Clin Oncol. 2012;30(33):4098-4103

## 14.16 Appendix P: List of prohibited concomitant medications and concomitant medications requiring caution for ceritinib

### Table 14-13 Prohibited medications that are strong inducers or inhibitors of CYP3A, or CYP3A substrates with narrow therapeutic index, or sensitive CYP2C9 substrates with narrow therapeutic index**

| **CYP2C9 substrates with narrow therapeutic index** | | | |
|---|---|---|---|
| warfarin | phenytoin | | |
| **CYP3A4/5 substrates with narrow therapeutic index** | | | |
| astemizole* | diergotamine | pimozide | alfentanil |
| cisapride* | ergotamine | quinidine* | terfenadine* |
| cyclosporine | fentanyl | tacrolimus | sirolimus |

| | | | |
|---|---|---|---|
| **Strong CYP3A4/5 inhibitors** | | | |
| Macrolide antibiotics:<br>clarithromycin<br>telithromycin<br>troleandomycin | Antivirals:<br>indinavir<br>lopinavir<br>nelfinavir<br>ritonavir<br>saquinavir<br>tipranavir | Antifungals:<br>itraconazole<br>ketoconazole<br>posaconazole<br>voriconazole | Others:<br>conivaptan<br>elvitegravir<br>mibefradil<br>nefazodone |
| **Strong CYP3A/5 inducers** | | | |
| avasimibe | carbamazepine | phenobarbital | phenytoin |
| rifabutin | rifampin | St. John's wort | |

* Compounds with risk of QT prolongation
For an updated list of CYP2C substrates, CYP3A substrates, inhibitors and inducers, please reference the Novartis Oncology Clinical Pharmacology internal memo: drug-drug interactions (DDI) database, Oct 2010, which is compiled primarily from the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database.
**Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.
Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

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

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

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

**Table 14-15 List of prohibited enzyme-inducing anti-epileptic drugs**

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

**Table 14-16 List of prohibited QT prolonging drugs**

| Prohibited medications causing QTc prolongation | | | |
|---|---|---|---|
| **Antiarrhythmic:** | **Anticancer:** | **Antibiotic:** | **Antianginal:** |
| amiodarone | arsenic trioxide | azithromycin | bepridil |
| disopyramide | vavdetanib | clarithromycin* | **Antipsychotic:** |
| dofetilide | **Antihistamine:** | erythromycin* | chlorpromazine |
| flecainide | astemizole* | moxifloxacin | haloperidol* |
| ibutilide | terfenadine* | sparfloxacin | mesoridazine |
| procainamide | **Antimalarial:** | **Antinausea:** | pimozide |
| quinidine* | chloroquine | domperidone | thioridazine |
| sotalol | halofantrine | droperidol | **Opiate agonist:** |
| **Antilipemic:** | **Anti-infective:** | **GI stimulant:** | levomethadyl |
| probucol | pentamidine | cisapride* | methadone |
| **Antidepressant:** | | | |
| citalopram | | | |
| Please note: *CYP3A substrate<br>Source: Arizona Center for Education and Research on Therapeutics (CERT), Drugs that prolong the QT interval and/or induce Torsades de Pointes, .azcert.org/medical-pros/drug-lists/drug-lists.cfm | | | |

## 14.17 Appendix Q: Bayesian Adaptive Design

### 14.17.1 Introduction

This document outlines the adaptive design framework to be used for all trials within Novartis's Modular phase II program designed to link targeted therapy to patients with pathway activated tumors.

Although the selected tumor types may vary by trial, this document outlines the design and analysis approach based on 8 example tumor cohorts:

- Lung NSCL
- Bladder
- Breast
- Colorectal
- GIST
- HNSCC
- Ovarian
- Sarcoma

Other tumor types may be considered for trials if 1) 4 or more patients are enrolled in the cohort, and 2) a reasonable estimate of the clinical benefit rate is available.

The primary endpoint is clinical benefit rate (CBR) in each cohort, with clinical benefit being assessed at 16 weeks. All patients will receive the experimental treatment for that particular trial.

### 14.17.1.1 Primary Analysis

We let $Y_i$ be the response indicator for the $i^{th}$ subject, and let $R_g$ be the assumed probability of response within a control population and $\pi_g = \Pr(Y_i = 1 \mid g_i = g)$ be the underlying probability of response for group $g$ within the trial. We transform to the logit scale for modeling purposes. Let $\theta_g$ be the mean log odds treatment effect, i.e.:

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right).$$

Thus, $\theta_g$ is the group specific logistic regression coefficient for group g. The primary analysis is a set of group specific tests that $\theta_g>0$, meaning that the experimental treatment is better than the assumed control rate for that group. Thus, we wish to test the set of hypotheses.

$$H_{0g} : \theta_g \leq 0$$

$$H_{1g} : \theta_g > 0$$

We proceed in a Bayesian fashion, assigning a prior distribution (discussed below) and computing the posterior probability of $H_{1g}$ within each group g. If, at the final analysis,

$\Pr(\theta_g>0 \mid \text{data}) > 0.80$

Then group g will be declared a success (thus, the final analysis produces a separate decision for each group). The trial also allows for early stopping of groups, described below.

### 14.17.1.2 Trial Logistics

Each trial will enroll all available subjects in all cohorts for 2 years unless a cohort cap is reached, or a cohort is stopped early, or the trial is stopped early by Novartis. Each trial will enroll no more than 30 evaluable subjects in each cohort. Interim monitoring will be conducted starting after the first 30 patients are enrolled overall (across all cohorts), and continuing each 13 weeks thereafter till study enrollment closure. After that, one CBR analysis will be done after database lock. At each interim data review, response information for the various cohorts will be evaluated to determine the current $\Pr(\theta_g>0 \mid \text{data})$ within each cohort, with sufficiently high/low values used to stop the cohort for success/futility. A minimum of 10 patients will be required in a cohort before it may discontinue enrollment for futility, and a minimum of 15 patients are required before discontinuing a cohort for efficacy. If a cohort stops enrolling early, the remaining cohorts will continue until the end of 2 years or until the other cohorts reach their own early stopping criteria. The final analysis will occur after the database lock for the primary CSR.

Each trial will enroll subjects in all listed cohorts. In addition, should other cohorts be identified throughout the trial, the following mechanism will be used. If another cohort is identified, it will not be placed into the statistical analysis unless 3 subjects enroll within the cohort (thus, the trial may enroll multiple additional cohorts, but a cohort will only be added to the list if at least 3 patients enroll from that cohort). Thus, it is possible (but not viewed as

likely) that multiple additional cohorts may be added to the trial if the trial has sufficient enrollment in multiple additional cohorts. In addition to sufficient enrollment, the sponsor must have a reasonable estimate of the control clinical benefit rate.

Subjects within any cohort which does not reach the minimum enrollment will be excluded from the interim and final analyses. As the study continues, early interim data reviews may be based on fewer cohorts than later interim data reviews, as the interim data reviews will include whatever cohorts have satisfied the criteria at the time of the data review.

### 14.17.2 Statistical Modeling

We let $Y_i$ be the response indicator for the $i^{th}$ subject, and let $R_g$ be the probability of response within a control population and $\pi_g = \Pr(Y_i = 1 \mid g_i = g)$ be the underlying probability of response for group $g$ within the trial. We transform to the logit scale for modeling purposes. Let $\theta_g$ be the mean log odds treatment effect, i.e.:

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right)$$

The statistical design borrows information across groups with a hierarchical model. The hierarchical model allows dynamic borrowing of information between groups such that more borrowing occurs when the groups are consistent and less borrowing occurs when the groups differ. In this way, the model is a compromise between the two alternate extremes of either a completely pooled analysis or a separate analysis in each group. We additionally incorporate a clustering mechanism that allows borrowing within clusters but treats clusters separately. This minimizes borrowing across groups that are quite different in terms of CBR.

The purpose of such an analysis (discussed in more detail in the appendix) is to produce higher power or lower type I error in situations where we see some commonality (identical effects are not required) among the groups. The model will borrow more in situations where the groups appear similar than situations where the groups appear different.

#### 14.17.2.1 Hierarchical Model with Clustering

Our hierarchical approach involves two stages. The goal of both stages is to allow the data to drive the amount of borrowing across groups. If the data indicate a large amount of borrowing is appropriate (due to similar results), the model will borrow more and thus increase the overall power of the trial within each group. In contrast, if the data indicate a small amount of borrowing is appropriate (due to dissimilar results) the model will adjust and each group will stand more on its own. This “dynamic” borrowing property is distinct from other approaches which use a fixed informative prior or apriori assume an amount of borrowing across groups. Here the approach includes two stages to identify the appropriate amount of borrowing based on the data.

The first stage of model places the groups into distinct clusters. The purpose of this stage is to minimize borrowing of information across groups that appear to be quite different. Thus, for example, should 2 of the groups appear similar while the others differ significantly, the model may place a large probability on two clusters, one containing the two similar groups with the other containing the remaining groups. The model incorporates the uncertainty of the data in

this determination, producing a probability distribution over the possible clusterings. Thus, in our example, the model may consider it highly likely that the 2 similar groups are in one cluster with the remaining groups in another, but it would also retain lower probabilities on the possibility all groups are in one cluster (e.g. we are simply seeing differences in the two groups by chance) as well as other possibilities. The complete analysis averages over this uncertainty. This clustering approach is implemented through a Dirichlet Process Mixture (DPM) model, described in the appendix.

At the second stage, we place hierarchical models over the groups within each cluster (thus, conditional on the clustering, there is no borrowing of information across clusters, only within clusters). The hierarchical model assumes that the $\theta_g$ have an across groups distribution

$$\theta_g \sim N(\mu, \tau^2)$$

The across group mean μ and variance $\tau^2$ are unknown, and hence have a prior distribution which is combined with the data to produce estimates of μ and $\tau^2$.

The variance component $\tau$ controls the degree of borrowing among groups. Small values of $\tau$ result in a greater degree of borrowing while large values of $\tau$ correspond to less borrowing. The parameter $\tau$ is estimated using the data, so the observed between group variation is a key component of the model behavior.

Combined, the two stages allow groups with similar results to borrow information between them (they will have a high probability of being in the same cluster) while groups with different results with borrow far less information between them (they will have a low probability of being in the same cluster).

Details of the two stages may be found in the appendix.

### 14.17.3 Evaluation of Trial Success and Futility

Interim monitoring will occur after the first 30 patients are on the study for 16 weeks (112 days), then every 13 weeks thereafter till study enrollment closure. At each interim data review, the groups will be evaluated for early futility and early success by comparing posterior quantities for the response rate to pre-specified early stopping criteria.

#### 14.17.3.1 Early Futility

If there is less than 10% probability that the response rate in a group exceeds the historical rate $R_g$, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$\Pr(\pi_g > R_g) < 0.10.$$

A group is only eligible for early stopping once a minimum of 10 patients has been evaluated for response in that group.

#### 14.17.3.2 Early Success

If there is at least 95% probability that the response rate in a group exceeds the historical rate, then the group will stop enrollment early for success. Formally, enrollment will stop early for success if:

$$Pr(\pi_g > R_g) > 0.95.$$

A minimum of 15 subjects will need to be evaluated prior to declaring a group to be efficacious.

#### 14.17.3.3 Final Analysis

In addition, recall the final analysis will occur when both accrual and follow-up are complete in all groups, or after the database lock for the primary CSR. If, at the completion of the trial, there is at least 80% probability that the response rate in a group exceeds the historical rate, then the group will be considered a success. Formally:

$Pr(\pi_g > R_g) > 0.80$.

### 14.17.4 Simulation

We evaluated type I error and power for each of the 8 possible groups under a variety of possible "truths" indicating various possible true underlying probabilities within each group.

#### 14.17.4.1 Assumptions

Accrual – Two scenarios for the assumed two-year expected accrual are investigated: 1) 10 subjects per group and 2) 5 subjects per group. Note that these are averages, the actual number of available patients is simulated as a Poisson distribution with the specified mean. Also note that the group cap of 30 applies, and thus if the number of available patients in a group exceeds 30, only the first 30 available patients in that group will be enrolled in the study.

Dropouts – We assume no dropouts for the purpose of this simulation.

Control Rates –Table 14-17 shows the assumed control clinical benefit rates for each group.

**Table 14-17 Assumed control CBR values used in the simulations.**

| Tumor Type | Assumed Control Rate ($R_g$) |
|---|---|
| Lung LSCL | 0.45 |
| Bladder | 0.47 |
| Breast | 0.50 |
| Colorectal | 0.38 |
| GIST | 0.50 |
| HNSCC | 0.45 |
| Ovarian | 0.47 |
| Sarcoma | 0.40 |

We consider four possible scenarios, or possible "truths" in the simulation. These consisted of a null scenario (where the treatment has no effect for any group), an alternative scenario (where the treatment is effective in all groups), a scenario where the treatment was effective in two of the groups, and a scenario where the treatment was effective in half of the groups.

Treatment Rates - The treatment rates for each scenario are shown in the table below. Values identical to the control are shown in bold, while values greater than the assumed control rate are shown in italics.

| | **Null** | **Alternative** | **Two** | **Half** |
|---|---|---|---|---|
| Lung LSCL | **0.45** | *0.71* | **0.45** | **0.45** |
| Bladder | **0.47** | *0.73* | **0.47** | **0.47** |
| Breast | **0.50** | *0.75* | **0.50** | **0.50** |
| Colorectal | **0.38** | *0.65* | **0.38** | **0.38** |
| GIST | **0.50** | *0.75* | **0.50** | *0.75* |
| HNSCC | **0.45** | *0.71* | **0.45** | *0.71* |
| Ovarian | **0.47** | *0.73* | *0.73* | *0.73* |
| Sarcoma | **0.40** | *0.67* | *0.67* | *0.67* |

Simulation Details – For each scenario we simulated 1000 trials. For each interim within each trial, we ran 50,000 MCMC iterations after a 1,000 MCMC iteration burnin.

### 14.17.4.2 Results

A total of 8 scenarios were simulated (two accrual scenarios and four possible 'truths' for the clinical benefit rate). The probability of group success for each group is provided for each scenario in the below two tables.

Table 14-18 provides the probability of group success for each of the cohort – assuming expected accrual of 10 subjects/cohort and 5 subjects/cohort separately.

**Table 14-18 Probability of group success**

| **Two-year expected accrual: 10 subjects/cohort** | | | | |
|---|---|---|---|---|
| Group | Null | Alternative | Two | Half |
| Lung LSCL | **0.158** | *0.915* | **0.208** | **0.305** |
| Bladder | **0.131** | *0.918* | **0.232** | **0.322** |
| Breast | **0.147** | *0.909* | **0.233** | **0.312** |
| Colorectal | **0.138** | *0.921* | **0.200** | **0.276** |
| GIST | **0.162** | *0.921* | **0.233** | *0.826* |
| HNSCC | **0.139** | *0.906* | **0.217** | *0.834* |
| Ovarian | **0.145** | *0.929* | *0.786* | *0.829* |
| Sarcoma | **0.135** | *0.939* | *0.758* | *0.852* |

| **Two-year expected accrual: 5 subjects/cohort** | | | | |
|---|---|---|---|---|
| Group | Null | Alternative | Two | Half |
| Lung LSCL | **0.132** | 0.803 | **0.204** | **0.258** |
| Bladder | **0.140** | 0.830 | **0.196** | **0.265** |
| Breast | **0.160** | 0.807 | **0.232** | **0.261** |
| Colorectal | **0.135** | 0.794 | **0.194** | **0.278** |
| GIST | **0.155** | 0.826 | **0.212** | *0.688* |
| HNSCC | **0.140** | *0.820* | **0.190** | *0.657* |
| Ovarian | **0.151** | *0.819* | *0.587* | *0.652* |
| Sarcoma | **0.139** | *0.799* | *0.579* | *0.667* |

Entries in bold represent groups where the treatment effect is 0 (e.g. the treatment is ineffective). Thus, entries in bold are type I errors. Entries in italics appear where the treatment is effective, and thus indicate the power of the design.

Generally, type I error is controlled below 0.20 under the null scenario (the borrowing compensates for the multiple interim data reviews) and power is an increasing function of the expected sample size (power is higher in the higher accrual situation across treatment rate scenarios). In the alternative scenario there remains decently high probability of success even in the lower accruing situations. When fewer groups are effective in truth, the scenarios "half" and "two" are harder to discern. Note in any particular trial there should be a mix of high and low enrolling groups, thus some groups may enroll closer to 10 subjects while others may only enroll five. This would produce a power value somewhere between the two tables.

Power is reduced and type I error is inflated when the truth is a mixture of effective and ineffective treatment effects across the groups. Generally power is a function of the sample size.

## Appendix 1 - Modeling Details

Recall at the first stage the groups are clustered according to a Dirichlet Process Mixture Model.

The number of clusters is not assumed to be known in advance but will instead be inferred from the data using Dirichlet Process Mixtures (DPM). The DPM looks across all the possible clusterings of the groups and assigns a probability to each based on the data. The prior distribution in a DPM is governed by a parameter α. When α is small, the prior favors large clusters. As α tends to zero, the prior tends to place all its mass on a single cluster containing all the groups. As α increases, the prior places more mass on clusterings with a large number of clusters. As α becomes very large, the prior places all of its mass on having a separate cluster for each group (that is, no borrowing across groups). Thus, by specifying extreme values of the prior one could force the groups into one cluster or force the groups to be analyzed in separate clusters. Here we choose a moderate version of α=2 (common values might be anywhere between 0.5 and 5) and allow the data more control over the clustering.

The details of the prior are as follows. Let $z_g$ represent the cluster to which group $g$ belongs. Then $z_g \sim$ Categorical($\boldsymbol{p}$), where $\boldsymbol{p}$ is the vector such that $p_k$ is the probability that a group belongs to cluster $k$ and $\sum_{k=1}^{\infty} p_k = 1$. We construct $\boldsymbol{p}$ using a stick-breaking process:

$$p_k = \beta_k \prod_{i=1}^{k-1} (1 - \beta_i)$$

and

$$\beta_k \sim \text{Beta}(1, \alpha).$$

A large value of $\alpha$ thus removes a very small amount of probability for $\boldsymbol{p}$, resulting in many clusters, while a small value of α tends to produce probabilities near 1 for the first cluster.

Conditional on the clustering, we fit a hierarchical model which has an across groups distribution

$$\theta_g \sim N(\mu, \tau^2)$$

As discussed above, this across group distribution states that within a cluster we expect to see some variation in the parameters, with that variation governed by τ. When τ is small, there is minimal variation across groups within a cluster, and thus within the cluster the model would approach pooling. In contrast, when τ is large we expect large amount of across group variation, and thus even though the groups are in the same cluster the $\theta_g$ values may be quite different. Apriori we have no way of knowing τ, so we estimate it using the data combined with the prior distributions

$$\mu \sim N(0, 1.82)$$

and

$$\tau^2 \sim IG(3,0.5),$$

where *IG(α, β)* is the inverse gamma distribution defined by:

$$f(x|\alpha,\beta) = \frac{\beta^\alpha e^{-\beta/x}}{x^{\alpha+1}\Gamma(\alpha)}.$$

When the entire model is implemented (via Markov Chain Monte Carlo) we consider the full joint distribution of the clustering combined with the hierarchical model parameters. We average over the entire range of the uncertainty in the parameters to produce the posterior distribution for each group parameter $\theta_g$, which is then used to drive the decisions in the model.