NOVARTIS

Clinical Development

LDK378

Protocol CLDK378A1201 / NCT02450903

A phase II, multi-center, open-label, single-arm study to evaluate the efficacy and safety of oral LDK378 treatment for patients with ALK-positive non-small cell lung cancer previously treated with alectinib

Authors	[redacted]
Document type	Amended Protocol Version
EUDRACT number	Not applicable
Version number	04 (Clean)
Development phase	II
Document status	Final
Release date	28-Jul-2016

Property of Novartis
Confidential
May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis

Template version 02-Dec-2013

[redacted]

Table of contents

Table of contents 2
List of appendices 7
List of figures 7
List of tables 7
List of abbreviations 9
Glossary of terms 12
Amendment 4 (28-Jul-2016) 13
Amendment 3 (30-Mar-2016) 15
Amendment 2 17
Amendment 1 18
Protocol summary 20
1 Background 23
1.1 Overview of disease pathogenesis, epidemiology and current treatment 23
1.1.1 Locally advanced or metastatic non-small cell lung cancer (NSCLC) 23
1.1.2 Targeted therapies in NSCLC 23
1.1.3 ALK positive NSCLC 24
1.2 Introduction to investigational treatment(s) and other study treatment(s) 25
1.2.1 Overview of LDK378 25
2 Rationale 35
2.1 Study rationale and purpose 35
2.2 Rationale for the study design 36
2.3 Rationale for dose and regimen selection 36
2.4 Rationale for choice of combination drugs 37
2.5 Rationale for choice of comparators drugs 37
3 Objectives and endpoints 37
4 Study design 40
4.1 Description of study design 40
4.1.1 Screening 40
4.1.2 Treatment duration 41
4.1.3 Follow-up period 41
4.2 Timing of interim analyses and design adaptations 42
4.3 Definition of end of the study 42
4.4 Early study termination 42
5 Population 42

[redacted]

5.1 Patient population 42
5.2 Inclusion criteria 42
5.3 Exclusion criteria 44
6 Treatment 47
6.1 Study treatment 47
6.1.1 Dosing regimen 47
6.1.2 Guidelines for continuation of treatment 48
6.1.3 Treatment duration 48
6.1.4 Definition of treatment cycle 48
6.2 Dose escalation guidelines 48
6.3 Dose modifications 49
6.3.1 Dose modification and dose delay 49
6.3.2 Treatment interruption and treatment discontinuation 49
6.3.3 Criteria for LDK378 dose modifications 50
6.3.4 Follow-up for toxicities 57
6.3.5 Anticipated risks and safety concerns of the study treatment 61
6.4 Concomitant medications 61
6.4.1 Permitted concomitant therapy 62
6.4.2 Prohibited concomitant therapy 63
6.5 Patient numbering, treatment assignment or randomization 65
6.5.1 Patient numbering 65
6.5.2 Treatment assignment 65
6.5.3 Treatment blinding 65
6.6 Study drug preparation and dispensation 66
6.6.1 Study drug packaging and labeling 66
6.6.2 Drug supply and storage 66
6.6.3 Study drug compliance and accountability 66
6.6.4 Disposal and destruction 67
7 Visit schedule and assessments 67
7.1 Study flow and visit schedule 67
7.1.1 Screening 72
7.1.2 Treatment period 73
7.1.3 Discontinuation of study treatment 73
7.1.4 Withdrawal of consent 75
7.1.5 Follow up period 75
7.2 Assessment types 76

[redacted]

7.2.1 Efficacy assessments 76
7.2.2 Safety and tolerability assessments 78
[redacted] [redacted] 82
[redacted] [redacted] 82
7.2.5 Resource utilization 84
7.2.6 Patient reported outcomes 85
8 Safety monitoring and reporting 85
8.1 Adverse events 85
8.1.1 Definitions and reporting 85
8.1.2 Laboratory test abnormalities 86
8.1.3 Adverse events of special interest 87
8.2 Serious adverse events 87
8.2.1 Definitions 87
8.2.2 Reporting 87
8.3 Emergency unblinding of treatment assignment 88
8.4 Pregnancies 88
8.5 Warnings and precautions 89
8.6 Data Monitoring Committee 89
8.7 Steering Committee (SC) 89
9 Data collection and management 89
9.1 Data confidentiality 89
9.2 Site monitoring 90
9.3 Data collection 90
9.4 Database management and quality control 91
10 Statistical methods and data analysis 91
10.1 Analysis sets 92
10.1.1 Full Analysis Set 92
10.1.2 Safety Set 92
10.1.3 Per-Protocol Set 92
10.1.4 Dose-determining analysis set 92
[redacted] [redacted] 92
10.2 Patient demographics/other baseline characteristics 92
10.3 Treatments (study treatment, concomitant therapies, compliance) 92
10.4 Primary objective 92
10.4.1 Variable 93
10.4.2 Statistical hypothesis, model, and method of analysis 93

[redacted]

10.4.3 Handling of missing values/censoring/discontinuations 93
10.4.4 Supportive analyses 93
10.5 Secondary objectives 93
10.5.1 Key secondary objective(s) 93
10.5.2 Other secondary efficacy objectives 94
10.5.3 Safety objectives 95
[redacted] 96
[redacted] 96
[redacted] 97
10.7 Interim analysis 98
10.8 Sample size calculation 98
10.9 Power for analysis of key secondary variables 98
11 Ethical considerations and administrative procedures 98
11.1 Regulatory and ethical compliance 98
11.2 Responsibilities of the investigator and IRB/IEC/REB 98
11.3 Informed consent procedures 99
11.4 Discontinuation of the study 99
11.5 Publication of study protocol and results 99
11.6 Study documentation, record keeping and retention of documents 99
11.7 Confidentiality of study documents and patient records 100
11.8 Audits and inspections 100
11.9 Financial disclosures 100
12 Protocol adherence 101
12.1 Amendments to the protocol 101
13 References (available upon request) 102
14 Appendices: 104
14.1 Appendix 1: List of prohibited concomitant medications and concomitant medications requiring caution for LDK378 104
15 Appendices 107
15.1 Appendix 2: Harmonization of efficacy analysis of solid tumor studies (RECIST 1.1) 107
15.1.1 Introduction 109
15.1.2 Efficacy assessments 109
15.1.3 Definitions 109
15.1.4 Disease measurability 109
15.1.5 Eligibility based on measurable disease 110
15.1.6 Methods of tumor measurement - general guidelines 110

[redacted]

15.1.7 Baseline documentation of target and non-target lesions 112
15.1.8 Follow-up evaluation of target and non-target lesions 112
15.1.9 Follow-up and recording of lesions 113
15.1.10 Non-nodal lesions 113
15.1.11 Nodal lesions 113
15.1.12 Determination of target lesion response 114
15.1.13 Determination of non-target lesion response 116
15.1.14 New lesions 116
15.1.15 Evaluation of overall lesion response 117
15.1.16 Efficacy definitions 118
15.1.17 Best overall response 118
15.1.18 Time to event variables 120
15.1.19 Progression-free survival 120
15.1.20 Overall survival 120
15.1.21 Time to progression 121
15.1.22 Time to treatment failure 121
15.1.23 Duration of response 121
15.1.24 Time to response 122
15.1.25 Definition of start and end dates for time to event variables 123
15.1.26 Handling of patients with non-measurable disease only at baseline 124
15.1.27 Sensitivity analyses 125
15.1.28 Data handling and programming rules 127
15.1.29 Study/project specific decisions 127
15.1.30 End of treatment phase completion 127
15.1.31 End of post-treatment follow-up (study phase completion) 128
15.1.32 Medical validation of programmed overall lesion response 128
15.1.33 Programming rules 129
15.1.34 Calculation of ‘time to event’ variables 129
15.1.35 Incomplete assessment dates 129
15.1.36 Incomplete dates for last known date patient alive or death 129
15.1.37 Non-target lesion response 130
15.1.38 Study/project specific programming 130
15.1.39 Censoring reason 130
15.1.40 References (available upon request) 131

[redacted]

List of appendices

Appendix 1: List of prohibited concomitant medications and concomitant medications requiring caution
Appendix 2: Harmonization of efficacy analysis of solid tumor studies (RECIST 1.1)

List of figures

Figure 4-1 Study design 40

List of tables

Table 1-1 All grades (at least 10%) and grade 3-4 adverse events, regardless of study drug relationship, by preferred term in patients treated in the 750 mg dose group (Safety Set) (Data cut-off: 14-April-2014) 30
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) (Data cut-off: 14-April-2014) 32
Table 1-3 Analysis of duration of response based on investigator assessment in NSCLC patients in the 750 mg dose group using Kaplan-Meier method, by prior ALK inhibitor status (Full Analysis Set – NSCLC 750 mg– Confirmed CR or PR) (Data cut-off: 14-Apr-2014)..... 32
Table 1-4 Analysis of PFS based on investigator assessment in NSCLC patients in the 750 mg dose group, by prior ALK inhibitor status (Full Analysis Set – NSCLC 750 mg) (Data cut-off : 14-Apr-2014).... 33
Table 3-1 Objectives and related endpoints..... 38
Table 6-1 Dose and treatment schedule..... 48
Table 6-2 Dose reduction steps for LDK378..... 50
Table 6-3 Criteria for interruption and re-initiation of LDK378 treatment..... 51
Table 6-4 Follow-up evaluations for selected toxicities..... 61
Table 7-1 Visit evaluation schedule 68
Table 7-2 Imaging assessment collection plan..... 78
Table 7-3 WHO performance status scale 79
Table 7-4 Local clinical laboratory parameters collection plan 80
Table 7-5 Local ECG collection plan..... 81
[redacted] [redacted] 84
Table 10-1 Operating characteristics for various ORRs when N=20 patients..... 98
Table 14-1 Prohibited medications that are strong inducers or inhibitors of CYP3A, or CYP3A substrates with narrow therapeutic index, or sensitive CYP2C9 substrates with narrow therapeutic index**..... 104

[redacted]

Table 14-2 List of medications to be used with caution 105
Table 14-3 List of prohibited enzyme-inducing anti-epileptic drugs 105
Table 14-4 List of prohibited QT prolonging drugs 106
Table 15-1 Response criteria for target lesions 114
Table 15-2 Response criteria for non-target lesions 116
Table 15-3 Overall lesion response at each assessment 117
Table 15-4 Overall lesion response at each assessment: patients with non-target disease only 124
Table 15-5 Options for event dates used in PFS, TTP, duration of response 126

[redacted]

List of abbreviations

AE	Adverse event
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma (serum, or blood) concentration versus time curve
AUCinf	Area under the plasma (serum, or blood) concentration versus time curve from time zero to infinity
AUCtau	Area under the plasma (serum, or blood) concentration versus time curve from time zero to end of dosing period
AUClast	Area under the concentration-time curve from time zero to the last measurable concentration time
BLRM	Bayesian logistic regression model
BUN	Blood Urea Nitrogen
CI	Confidence interval
CL/F	Apparent clearance
Cmax	Maximum (peak) concentration of in plasma
Cmin	Minimum (trough) concentration of drug in plasma
CNS	Central nervous system
CR	Complete response
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DCR	Disease control rate
D	Entered into database
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DOR	Duration of response
DS&E	Safety & Epidemiology
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
EML4-ALK	Echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase
EOS	End of study
EOT	End of treatment

[redacted]

FAS	Full analysis set
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FSH	Follicle-stimulating hormone
GGT	Gamma-glutamyl transpeptidase
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
IB	Investigator's brochure
IC50	Half maximal (50%) inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IGF1R	Insulin-like Growth Factor 1 Receptor
INR	International normalized ration
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous(ly)
LFT	Liver function test
LH	Luteinizing hormone
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N/A	Not applicable
NSAIDs	Non-steroidal, anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
OIRR	Overall intracranial response rate
ORR	Overall response rate
OS	Overall survival
[redacted]	[redacted]
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetics
PR	Partial response
PS	Performance Status
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia formula
QD	quaque diem/once daily
RAP	Report and Analysis Plan
RBC	Red blood count

[redacted]

RD	Recommended dose
RECIST	Response Evaluation Criteria In Solid Tumors
R Value	ALT/ALP in x ULN
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Stable disease
SEC	Safety event categories
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SHBG	Sex hormone binding globulin
SUSARs	Suspected unexpected serious adverse reactions
TKIs	Tyrosine kinase inhibitors
TTIR	Time to intracranial response
TTR	Time to response
ULN	Upper limit of normal
VATS	Video-assisted thoracic surgery
VEGF-A	Vascular endothelial growth factor-A
WBC	White blood cells
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient.
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q 21 days).
Dose level	The dose of drug given to the patient (total daily or weekly etc.).
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., before starting any of the study procedures described in the protocol).
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug".
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage.
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study.
Patient number	A unique identifier number (consisting of the center number and a patient-specific number) assigned to each patient who enrolls in the study.
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study treatment	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any combination or control drug(s).
Study treatment discontinuation	Point/time when a patient permanently discontinues study treatment for any reason.
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	A quantity subject to variation of values used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

[redacted]

Amendment 4 (28-Jul-2016)

Amendment rationale

As of 27-June-2016, 9 patients have been enrolled.

[redacted]

In addition, blood sample can be collected in the event that a patient experiences an AE which requires either dose modification or termination from the study medication, QT interval prolongation or hepatotoxicity, as needed.

Changes to the protocol

[redacted]

- Section 6.4.2.1: update the immunotherapy in the section of Other anticancer therapy in Prohibited concomitant therapy.

[redacted]

- Section 7.2.4.1: correct the language.

[redacted]

[redacted]

IRB/IEC/REB 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.

[redacted]

Amendment 3 (30-Mar-2016)

Amendment rationale

As of 25-Mar-2016, 6 patients have been enrolled.

The purpose of this amendment is to extend the enrollment also to the patients who received prior crizotinib in addition to alectinib. In addition it is clarified that alectinib doesn't need t o be the last therapy prior to study enrollment, and no specific sequence of prior alectinib and crizotinib is required for enrollment.

The reason for this change is that despite alectinib recent approval in Japan as 1 st line therapy for ALK-positive NSCLC, the vast majority of patients in Japan have received crizotinib as 1st line therapy and alectinib as next line. Therefore, this amendment has been released in order to improve the feasibility of the study.

As shown in Section 1.2.1.2.2, in study CLDK378X2101 five patients previously treated with both crizotinib and alectinib, received LDK378; a confirmed PR was observed in two out of the five patients.

Changes to the protocol

- Section 1.2.1: update the ZYKADIA approval status.
- Section 1.2.1.2.2: update the additional clinical data.
- Section 2.1: update the additional clinical data.
- Section 2.2: update the information.
- Section 4.1.1: update to allow the enrollment of patients pre-treated with crizotinib as prior ALK inhibitor therapy in addition to alectinib.
- Section 4.3: update the language to clarify the definition of end of the study
- Section 5.1: update the language to clarify the patient population.
- Section 5.2 Inclusion criteria #4: inclusion criteria #4 has been replaced by inclusion criteria #4a to update the crizotinib as prior allowed therapy.
- Section 5.2 Inclusion criteria #5: inclusion criteria #5 has been replaced by inclusion criteria #5a to update the crizotinib as prior allowed therapy.
- Section 5.2 Inclusion criteria #12: inclusion criteria #12 has been replaced by inclusion criteria #12a to update the performance status.
- Section 5.3 Exclusion criteria #3: exclusion criteria #3 has been replaced by exclusion criteria #3a to update the crizotinib as prior allowed therapy.
- Section 5.3 Exclusion criteria #4: exclusion criteria #4 has been replaced by exclusion criteria #4a to update the crizotinib as prior allowed therapy.
- Section 8.2.2: update the language of SAE reporting.

[redacted]

IRB/IEC/REB 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.

[redacted]

Amendment 2

Amendment rationale

As of the release date of this amendment, 4 patients have been enrolled.

The amendment provides follow up evaluations for hepatic toxicities and work -up guidelines for potential Drug Induced Liver Injury (DILI) cases. For consistency with other Novartis sponsored clinical studies, other changes were implemented in this amendment:

Exclusion criteria for contraception use is being updated

Dose guidance modification for QTcF text was updated to provide clarification on monitoring procedure.

Changes to the protocol

- Section 5.3 Exclusion criterion # 18 (contraception): updated the definition of highly effective contraception
- Table 6-3: updated criteria for interruption and re-initiation of LDK378 treatment for AST or ALT and concurrent total bilirubin elevation and electrocardiogram QT corrected (QTcF) interval prolonged.
- Section 6.3.4.2: updated to include information for identifying potential drug-induced liver injury.
- Table 14-4: Added medication to reflect updated List of prohibited medication causing QTc prolongation.

IRB/IEC/REB 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

[redacted]

In addition, this amendment has been implemented to provide updated safety information as well as clarification of sections of the protocol where additional guidance was required.

Changes to the protocol

- Section 1.1: updated for editorial change.
- Section 1.2.1: updated the status of marketing authorization application (MAA) submission to health authorities.
- Section 1.2.1.2: editorial change to "adverse events of special interest" to ensure consistency between this section and Section 8.1.3.
- Section 1.2.1.2.2: editorial change.
- [redacted]
- Section 5.1: corrected typographical error "rescreening of patients during the screening period will **not** be allowed".
- Section 5.2 Inclusion criterion # 10 (serum amylase): updated serum amylase criterion.
- Section 5.3 Exclusion criterion #10 (pancreatitis): added the pancreatic disease criterion.
- Section 6.3: updated to clarify the dose modification depending on the AE grade and changed period for LDK378 treatment interruption.
- Table 6-3 : updated criteria for interruption and re-initiation of LDK378 treatment.
- Section 6.3.4.8: added guidelines for laboratory assessment of pancreatic abnormalities.
- Table 6-4 (pancreatic): added follow-up evaluations for selected toxicities
- Section 6.4.1.1: clarified dose modification guidelines for corticosteroids and treatment interruption guidelines for LDK378.
- Section 6.4.1.2: modified the guidelines for bisphosphonates treatment during the study.
- Section 6.4.1.5: clarified guidelines for interruption and re-initiation of LDK378 treatment before and after radiotherapy/surgery.
- Section 6.4.2.6: clarified that CYP2C9 and CYP3A4/5 substrates with narrow therapeutic index are not permitted for concomitant use with LDK378.
- Section 6.5.1: removed the sentence related to the central enrollment system which is not used in this study.
- [redacted]
- Section 7.1.1.3: removed the "FDA-approved".
- Section 7.1.5.2: removed the phrase "start of new anti-cancer therapy".

[redacted]

- Section 7.2.2.6.1: clarified ECG instructions and specified ECG reader qualification requirements.
- Table 7-7 (Plasma): clarified the time point.
- Section 8.1.3: updated for editorial change.
- Section 13: updated 2 references, “Crizotinib a novel and first-in-class multitargeted tyrosine kinase inhibitor for the treatment of anaplastic lymphoma kinase rearranged non-small cell lung cancer and beyond. Drug Des Devel Ther” and “Fusion of EML4 and ALK is associated with development of lung adenocarcinomas lacking EGFR and KRAS mutations and is correlated with ALK expression. Mol Cancer”.

IRB/IEC/REB Approval

A copy of this amended protocol will be s ent 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:

Protocol number	CLDK378A1201
Title	A phase II, Multi-center, Open-label, Single-Arm Study to Evaluate the Efficacy and Safety of Oral LDK378 Treatment for Patients with ALK-Positive Non-Small Cell Lung Cancer previously treated with alectinib.
Brief title	To evaluate efficacy and safety of LDK378 in patients with ALK positive NSCLC previously treated with alectinib.
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Alectinib was approved in Jul 2014 in Japan and it has been used widely as a first-line ALK-TKI therapy. However clinical experience of LDK378 in patients who failed alectinib therapy remains very limited. Therefore we will evaluate the antitumor activity and safety profile of LDK378 when used as a single agent in patients with ALK-rearranged locally advanced or metastatic NSCLC who have been pretreated with alectinib.
Primary Objective(s) and Key Secondary Objective	Primary objective: To demonstrate the antitumor activity of LDK378, as measured by overall response rate (ORR) to LDK378 by investigator assessment. Key secondary objectives: To evaluate response related endpoints as assessed by investigator: disease control rate (DCR), time to response (TTR), duration of response (DOR).
Secondary Objectives	• To evaluate progression-free survival (PFS). • To evaluate overall survival (OS). • To evaluate overall intracranial response rate (OIRR). • To evaluate the safety profile of LDK378.
Study design	This is a single-arm, open-label, multicenter, phase II study to evaluate the efficacy and safety of the ALK inhibitor LDK378 when used as single agent in patients with ALK-rearranged stage IIIB or IV NSCLC previously treated with alectinib. A total of approximately 20 patients will be enrolled into the study to receive oral LDK378. Treatment with LDK378 750 mg qd will continue until the patient experiences disease progression as determined by the investigator according to RECIST 1.1, unacceptable toxicity that precludes further treatment, pregnancy, start of a new anticancer therapy, discontinues treatment at the discretion of the patient or investigator, lost to follow-up, death, or study is terminated by Sponsor. LDK378 may be continued beyond RECIST-defined PD as assessed by the investigator, if in the judgment of the investigator, there is evidence of clinical benefit. In these patients tumor assessment should continue as per the schedule of assessments until treatment with LDK378 is permanently discontinued. Patients who discontinue the study medication in the absence of progression will continue to be followed for tumor assessment until the time of PD as assessed by the investigator.
Population	This study will be conducted in adult male or female patients, with ALK-rearranged (as determined by Vysis ALK Break Apart FISH Probe kit [Abbott Molecular Inc.]), advanced (stage IIIB or IV) NSCLC who have progressed since prior therapy with alectinib. Prior crizotinib and/or up to one regimen of cytotoxic chemotherapy are allowed.

[redacted]

Main Inclusion criteria	• Histologically or cytologically confirmed diagnosis of Stage IIIb or IV NSCLC that carries an ALK rearrangement as determined locally by Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test. If documentation of ALK rearrangement is not available as described above, a test to confirm ALK rearrangement must be performed locally by Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) prior to study. • Patients must have NSCLC that has progressed at study enrollment. • Patients must have received previous treatment with alectinib for treatment of locally advanced or metastatic NSCLC. Prior therapy with crizotinib as ALK inhibitor therapy in addition to alectinib is allowed. Alectinib doesn't need to be the last therapy prior to study enrollment. No particular sequence of prior alectinib and crizotinib is required for enrollment. • A minimum of 21 days of treatment with alectinib will be required to qualify as one prior course of alectinib (unless alectinib was discontinued due to PD after a shorter treatment course). • Patients may have discontinued alectinib therapy for disease progression, intolerance or other reason. • Patients must be chemotherapy-naïve or have received only one line of prior cytotoxic chemotherapy. If patients received chemotherapy, such patients must have progressed during or after the last chemotherapy regimen received prior to the first dose of LDK378. • Age 18 years or older at the time of informed consent. • Patients must have a tumor tissue sample available, as an archival sample (collected either at the time of diagnosis of NSCLC or any time since) [redacted] • Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v 4.03). Patients with grade ≤ 2 peripheral neuropathy or any grade of alopecia, fatigue, nail changes or skin changes are allowed to enter the study.
Main Exclusion criteria	• Patients with known hypersensitivity to any of the excipients of LDK378. • Prior therapy with other ALK inhibitor investigational agents except crizotinib and alectinib. • Prior systemic anti-cancer (including investigational) therapy aside from alectinib, crizotinib and one regimen of previous cytotoxic chemotherapy for locally advanced or metastatic NSCLC. • Patients with symptomatic central nervous system (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. • Patient has history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis. • Corrected QT (QTcF) > 470 msec using Fridericia's correction on the screening ECG (as mean of triplicate ECGs).
Investigational and reference therapy	LDK378
Efficacy assessments	Tumor assessment by RECIST 1.1 as evaluated by investigator.

[redacted]

Safety assessments	• Hematology, chemistry, urinalysis, coagulation, pregnancy test and hormones (males only) • ECG • Performance status • Vital signs • Physical examination • Adverse events
[redacted]	
Data analysis	The study does not include formal statistical hypothesis testing and the sample size is not derived based on power considerations. With a sample size of 20 patients, there is an approximately 58.4% chance that the exact 95% confidence interval (CI) will exclude an insufficient response rate of 10% when the true ORR is 30%. For an observed response rate of 30.0% (6 responders in 20 patients), the exact 95% CI is (11.9%, 54.3%). The ORR will be estimated and reported along with the exact 95% CI. No statistical hypothesis testing is planned. DCR and OIRR will be analyzed in a similar way to the ORR. DOR, PFS and OS will be described using Kaplan-Meier methods and relevant summary statistics. TTR will be summarized using descriptive statistics for patients with a confirmed response. Adverse events, laboratory abnormalities and notable ECGs will be tabulated.
Key words	ALK, NSCLC, LDK378

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

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

Lung cancer has been the most common cancer in the world for several decades. In Worldwide, lung cancer occurred in approximately 1.8 million patients in 2012 and caused an estimated 1.6 million deaths. (Brambilla et al 2014). In 2012, approximately 160,000 deaths due to lung cancer were expected in the United S tates (US; Siegel et al 2012) and 262,000 in the European Union (EU; Malvezzi et al 2012) and about 70,000 in Japan (MHLW-Population survey report 2013).

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

Cigarette smoking remains the most important risk factor for lung cancer, although approximately 15% of all lung cancers are diagnosed in patients who never smoked.

The high mortality rate of lung cancer could be explained in an advanced stage for most cases; only 25-30% of new NSCLC cases are diagnosed with localized disease that is potentially curable with surgery (Nguyen et al 2012). The majority of patients are diagnosed with locally advanced or metastatic disease, for which surgery is not indicated and which do not fit indications for surgery.

As summarized in the current National Comprehensive Cancer Network (NCCN) Guidelines for NSCLC, platinum-based combination chemotherapy is superior to best supportive care for patients with advanced, incurable disease (NCCN Guidelines® v13 2014). Platinum-doublets chemotherapy (cisplatin or carboplatin in combination with other chemotherapy agents, with or without bevacizumab) is standard firstline treatment of locally advanced or metastatic NSCLC, unless a patient has a known “druggable” gene mutation or aberration, and is therefore a candidate for a targeted therapy (as discussed below).

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

1.1.2 Targeted therapies in NSCLC

During the last few years, improvement in the knowledge of NSCLC biology has led to the identification of molecular events crucial for malignant transformation and cancer cell survival. These aberrant molecular events serve as critical oncogenic drivers for these cancers

[redacted]

and, therefore represent potential therapeutic targets (Gettinger and Lynch 2011). As a result, new targeted treatment options for these patients are evolving. Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor-A (VEGF-A), and erlotinib an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), have been approved for the treatment of NSCLC (Gettinger and Lynch 2011).

The case of EGFR TKIs illustrates a new paradigm in the treatment of NSCLC. There is increasing evidence that activating mutations of EGFR define a small subset of patients with NSCLC who have sensitivity to EGFR TKIs (Ettinger et al 2010). Six randomized trials have demonstrated that patients harboring activating EGFR mutations benefit more from EGFR TKIs than from standard chemotherapy in terms of response rate, progression free survival, toxicity profile, and quality of life. In particular, the success of EGFR TKIs highlights the importance of identifying specific molecular drivers of NSCLC to appropriately direct targeted agents in specific patient populations.

1.1.3 ALK positive NSCLC

Another clinically relevant molecular subset of NSCLC is driven by recently the newly discovered echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) translocation.

ALK was first identified as a chromosome translocation-produced protein fusion in the majority of anaplastic large cell lymphomas (ALCL). When fused to other proteins, ALK becomes constitutively active, leading to increased catalytic kinase function, signal - transduction activity, and oncogenic function. Expression of EML4-ALK, a new fusion protein between ALK and the echinoderm microtubule-associated protein-like 4 (EML4) gene, in transgenic mice has been shown to induce tumor formation, suggesting the therapeutic potential of targeting the EML4-ALK fusion protein in NSCLC (Soda et al 2007). The frequency of EML4-ALK rearrangement in patients with NSCLC is relatively rare event; it is present in approximately 2-8% of tumors tested (Scagliotti et al 2012; Takeuchi et al 2009; Soda et al 2007).

Patients with ALK-rearranged NSCLC are similar to those with EGFR mutations (i.e., adenocarcinoma, nonsmokers or former smokers), up to 30% of smokers or former smokers has been included in the pivotal phase 3 study evaluating crizotinib after first line of treatment for ALK-rearranged NSCLC (Shaw et al 2013) except they are often younger. In addition, ALK rearrangements are found in patients with adenocarcinoma but not usually found in squamous cell or large cell carcinoma (Shaw et al 2009). ALK rearrangements and other oncogenic drivers such as mutant EGFR and oncogenic RAS are generally mutually exclusive, consistent with the notion that ALK rearrangement defines a unique molecular subset of NSCLC (Gainor et al 2013). In patients with adenocarcinoma lacking EGFR and KRAS mutations, the prevalence of EML4-ALK translocation could be as high as 42.8 % (Zhang 2010). In these patients, ALK rearrangements serve as a key strong oncogenic driver for NSCLC and represent a critical therapeutic target susceptible to targeted ALK kinase inhibition.

Crizotinib, an orally available small-molecule inhibitor of ALK and MET tyrosine kinases, is the first tyrosine kinase inhibitor to target ALK to have demonstrated a clinical activity . The

[redacted]

first evidence that ALK-positive NSCLC responds to ALK inhibitors was seen with crizotinib, an ALK and MET inhibitor, which in single-arm trials was shown to induce durable responses in 50-61% of patients. Based on these data, crizotinib received accelerated approval under the trade name Xalkori® in the US and conditional marketing authorization in the EU (Ou 2011). Subsequently, crizotinib received approval in Switzerland, Japan, China, Canada, as well as other countries worldwide. Advanced or metastatic ALK-positive NSCLC patients, after failure to a prior platinum-based chemotherapy, experienced a higher response rate (RR) to crizotinib (RR=65%; 95%CI:58-72) compared to chemotherapy (RR=20%; 95CI:14-26) and a longer progression free survival (PFS) if treated with crizotinib compared with second -line chemotherapy (7.7 months versus 3.0 months, HR=0.49; 95% CI, 0.37 – 0.64) (Shaw et al 2013). In addition, crizotinib showed a higher RR compared to chemotherapy (ORR= 74% versus 45%; P<0.0001) and a longer PFS (Median 10.9 months versus 7.0 months; HR: 0.454; 95% CI: 0.346–0.596) in treatment naive advanced non-squamous ALK-positive NSCLC patients (Mok et al 2014).

Alectinib, an orally available small-molecule inhibitor of ALK tyrosine kinases, has been approved in ALK-TKI naïve patients with advanced NSCLC in Japan in 2014. The results from Alectinib phase I/II study (CH5424802/RO5424802, [Chugai/Roche]) in ALK-TKI treatment naïve ALK-positive NSCLC were published (Seto et al 2013). In the phase I portion, 24 patients were treated at doses of 20-300 mg twice daily and no dose limiting toxicities (DLTs) were observed. In the phase 2 portion, 46 patients were treated with the recommended dose, 300 mg twice daily, of whom 43 (93.5%) achieved an objective response including two complete responses. Adverse events were reported in all 46 patients with main toxicities as follows: dysgeusia, increased aspartate aminotransferase (AST), increased blood bilirubin and increased blood creatinine. Grade 3 adverse events were reported in 17 (37%) patients, but no grade 4 adverse events or deaths were reported. The drug was generally well tolerated with manageable adverse events.

While crizotinib and alectinib has impressive activity in patients with ALK rearranged NSCLC and ALK-positive patients will receive crizotinib or alectinib, however these cancers invariably progress, with the development of resistance to crizotinib and alectinib. For the se patients there is limited alternative ALK-targeted therapy. Therefore, the development of ALK TKIs with clinical activity against ALK-positive NSCLC resistant to prior ALK-TKI is crucial.

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

1.2.1 Overview of LDK378

LDK378 [5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl) phenyl]-N4-[2 (isopropylsulfonyl) phenyl]-2,4-pyrimidinediamine] is an orally available ALK inhibitor. LDK378 is an approximately 20-fold more potent ALK inhibitor than crizotinib, it is more selective for ALK and does not inhibit MET.

In addition, LDK378 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 (wi th

[redacted]

and without previous crizotinib therapy) led to the approval of LDK378 (ceritinib) by the 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.

In the European Union, the trade name ZYKADIA™ was approved on 6-May-2015 for the following indication:

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

In Japan, the trade name ZYKADIA® was approved on 28-Mar-2016 for the following indication:

- "Unresectable advanced and/or recurrent anaplastic lymphoma kinase (ALK) fusion gene-positive non-small cell lung cancer with resistance or intolerance to crizotinib"

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

1.2.1.1 Non-clinical experience

1.2.1.1.1 Pharmacology

LDK378 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*. LDK378 is approximately 20-fold more potent than crizotinib in enzymatic inhibition assays of ALK kinase activity (Half maximal (50%) inhibitory concentration (IC_{50}) of 0.15 nM for LDK378 and 3 nM for crizotinib). In a kinase panel of 36 enzymes, LDK 378 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.

Preclinical data showed inhibition of the kinase activity of the NPM-ALK fusion oncogene (in Karpas299 human ALCL cells) and of the EML4-ALK fusion oncogene (in H2228 human NSCLC cells) with LDK378, which led to inhibition of cancer cell proliferation *in vitro*. Inhibition of the downstream signaling pathway by LDK378 correlated with inhibition of the proliferation. In addition, 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*. LDK378 was also active in the cell lines with ALK amplification or expression of activating point mutations.

[redacted]

1.2.1.1.2 Antitumor activity in xenograft models

LDK378 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 a nd Karpas299 ALCL cells, LDK378 dosed at 25 mg/kg daily, a dose below the maximum tolerated dose (MTD) in clinical studies defined in good laboratory practice (GLP) toxicity studies (30 mg/kg in monkey and 30 mg/kg in rat), resulted in regression of establ ished tumors. When dosed at 50 mg/kg daily for 14 days in the H2228 NSCLC model in mice, LDK378 resulted in complete and prolonged tumor regression (lasting for more than 4.5 months after treatment was discontinued). In the same experiments, crizotinib dosed at 100 mg/kg daily for 14 days resulted in complete tumor regression, but tumors relapsed within 2 weeks after stopping treatment.

LDK378 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 LDK378 may be clinically active in ALK -rearranged NSCLCs in multiple treatment settings.

1.2.1.1.3 Nonclinical pharmacokinetics (PKs) and metabolism

In general, LDK378 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. LDK378 is highly bound to plasma protein (>94%) in all species. Following oral administration of [^{14}C] LDK378 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 LDK378 was the major component in feces and bile of intact and bile duct -cannulated rats. In the rat, LDK378 underwent oxidation leading to the formation of four oxygenated metabolites (designated as M23.6, M30.6, M35.8, and M33.4). In addition, LDK378 underwent sulfation leading to M36.8 and oxidation followed by sulfation, resulting in the presence of M29.5. LDK378 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]-LDK378, LDK378-derived radioactivity was excreted predominantly via the fecal route (>99%), and renal excretion was a minor pathway for excretion (< 1%). Fecal excretion was the result of biliary excretion (69%) and gastrointestinal (GI) secretion (31%). Since parent drug was the major component in bile and feces after intravenous (i.v.) administration, enterohepatic circulation may occur.

CYP3A4/5 is the major hepatic enzyme metabolizing LDK378 in a human *in vitro* system. The metabolic drug-drug interaction (DDI) potential of LDK378 as an inhibitor was evaluated

[redacted]

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) "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations" and in EMA DDI guideline (2012) "Guideline on the Investigation of Drug Interactions", at clinically relevant concentrations, LDK378 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 LDK378. LDK378 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 LDK378 concentrations of up to 50 µM.

LDK378 is likely a P-gp, but not BCRP or MRP2 substrate. It does not inhibit P-gp, BCRP or MRP2 up to 1.5 µM *in vitro*.

1.2.1.1.4 Safety pharmacology and toxicology

LDK378 has moderately potent activity on the hERG channel with an IC_{50} of 0.4 µM. In a GLP implanted telemetry study in monkeys LDK378 at oral doses of 0, 10, 30 and 100 mg/kg in a cross-over design had no effects on blood pressure, heart rate, body temperature, or ECG intervals (PR, RR or QRS), and did not produce any arrhythmias. Apparent QT/QTc prolongation was noted in one animal between approximately 10 and 19 hours (ranged from 14.25 to 43.52 msec above pre-dose baseline value) post-dose after receiving the 100 mg/kg dose. No changes were noted in the central nervous system (CNS) and no effects on the respiratory system were observed in rats at single high doses (100 mg/kg).

LDK378 was evaluated for safety in repeated dose studies up to 26 weeks and 13 weeks in rats and monkeys, respectively. The principal toxicity related to LDK378 administration was inflammation of the extra hepatic 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 submucosa of rats and monkeys. 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 hepatocellular nectrosis (rat only), minimal increases in liver transaminases and vacuolation of the bile duct epithelium, as well as inflammatory cell infiltrate. The pancre as was a target organ in the rat, but not the monkey, with acinar cell atrophy and mixed cell inflammation noted at mid and high doses in the 4-week study. The pancreas was not affected in the 13- and 26-week studies. Alveolar foamy macrophages (confirmed phospholipidosis) were seen in the lungs of rats, but not in monkeys, and the lymph nodes of rats and monkeys had macrophage aggregates. Lymphoid depletion in the thymus was seen in monkey at overtly high doses Target organ effects showed partial to complete recovery during the non-dosing period.

In embryo-fetal toxicity studies in rats and rabbits, there was no evidence of embryolethality, fetotoxicity or teratogenicity at the maternal toxicity dose. However, the exposure at NOAEL for maternal toxicity and embryo-fetal development was lower than the clinical exposure in patients given 750 mg qd.

[redacted]

Preclinical studies (*in vitro* 3T3 NRU assay) indicated a low risk of phototoxicity with use of LDK378.However, a confirmatory assay from an *in vivo* ultraviolet local lymph node assay (UV LLNA) demonstrated no phototoxic potential with LDK378.

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety and tolerability

LDK378 is generally associated with a manageable safety profile.

In CLDK378X2101, as of the 14-April-2014 cut-off date, total of 255 ALK positive patients were enrolled 246 NSCLC (98.4%) and 9 Non-NSCLC (3.6%). For the 246 patients with ALK positive NSCLC treated at the recommended dose of 750 mg in this ongoing study, the median duration of exposure was 38.6 weeks (range 0.4 to 105.9). At least one dose reductions due to adverse events occurred in 61.8% of patients treated with LDK378 at the 750 mg dose. In 255 ALK positive patients, 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, constipation, and cough. The frequently occurred grade 3-4 Adverse events (AEs) (>5%), regardless of study drug relationship were ALT (Alanine aminotransferase) increased (29.8%), AST increased (9.8%), lipase increased (6.3%), diarrhea (5.9%), nausea (5.9%), hyperglycemia (5.9%), fatigue (5.1%), anaemia (5.1%) and blood alkaline phosphatase increased (5.1%) (Table 1-1).

[redacted]

Table 1-1 All grades (at least 10%) and grade 3-4 adverse events, regardless of study drug relationship, by preferred term in patients treated in the 750 mg dose group (Safety Set) (Data cut-off: 14-April-2014)

	LDK378 750 mg N=255	
	All Grades	Grade ¾
Preferred term	n (%)	n (%)
Total	255 (100.0)	206 (80.8)
Diarrhea	221 (86.7)	15 (5.9)
Nausea	211 (82.7)	15 (5.9)
Vomiting	157 (61.6)	12 (4.7)
Alanine Aminotransferase Increased	112 (43.9)	76 (29.8)
Fatigue	109 (42.7)	13 (5.1)
Abdominal Pain	98 (38.4)	3 (1.2)
Decreased Appetite	95 (37.3)	4 (1.6)
Aspartate Aminotransferase Increased	83 (32.5)	25 (9.8)
Constipation	79 (31.0)	0
Cough	73 (28.6)	0
Dyspnea	63 (24.7)	11 (4.3)
Abdominal Pain Upper	60 (23.5)	2 (0.8)
Asthenia	50 (19.6)	2 (0.8)
Back Pain	50 (19.6)	1 (0.4)
Headache	51 (20.0)	4 (1.6)
Weight Decreased	46 (18.0)	5 (2.0)
Blood Alkaline Phosphatase Increased	45 (17.6)	13 (5.1)
Blood Creatinine Increased	43 (16.9)	0
Pyrexia	42 (16.5)	0
Insomnia	39 (15.3)	0
Musculoskeletal Pain	37 (14.5)	0
Rash	34 (13.3)	0
Dyspepsia	32 (12.5)	1 (0.4)
Anemia	31 (12.2)	13 (5.1)
Dizziness	31 (12.2)	0
Hypokalemia	29 (11.4)	11 (4.3)
Edema Peripheral	27 (10.6)	0
Musculoskeletal Chest Pain	27 (10.6)	0
Non-Cardiac Chest Pain	26 (10.2)	2 (0.8)
Arthralgia	26 (10.2)	0

The most frequent AEs requiring dose adjustments or interruptions reported in ≥5% of the patients were: ALT increased, nausea, diarrhea, AST increased, vomiting, fatigue, abdominal pain, decreased appetite and lipase increased. AEs leading to study drug discontinuations occurred in 10.2% of patients treated with LDK378 at the 750 mg dose. The most frequent AEs (which occurred in two or more patients) leading to study drug discontinuations were

[redacted]

pneumonia, ALP increased, decreased appetite, general physical health deterioration, pneumonitis, and respiratory failure

Serious adverse events (SAEs) reported in 47.5 % of the 255 patients treated at the recommended dose of 750 mg were pneumonia, interstitial lung disease (ILD)/pneumonitis, convulsion, dyspnea, nausea, hyperglycemia, pericardial effusion and respiratory failure (incidence ≥2%). On treatment death except death due to the cancer occurred in 14 patients, consisting of: pneumonia and respiratory failure in 3 patients and acute respiratory failure, cardiac tamponade, gastric haemorrhage, ILD, pneumothorax, pulmonary tuberculosis, respiratory failure sepsis and septic shock (1 patient each). Adverse events of special interest to be monitored for LDK378 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 [Investigator's Brochure].

In Japanese phase I study with expansion phase, CLDK378X1101, total of 20 patients with ALK-rearranged tumor patients, 19 (95%) with NSCLC and 1 (5%) inflammatory myofibroblastic tumor were enrolled as of the 4-Jul-2014 cut-off date. The median duration of exposure was 32.1 weeks (range 0.1 to 86.7). In dose escalation phase, tolerability up to 750 mg/day was confirmed. All patients experienced ≥1 AE regardless of study drug relationship. The most common AEs were nausea (95%), diarrhea (75%) and vomiting (75%). Grade 3 or 4 AEs regardless of study drug relationship were reported in 16 patients. The most frequent grade 3 or 4 AEs were ALT increased and tumor pain, each of which occurred in two patients (10%) (Murakami et al 2014).

1.2.1.2.2 Clinical efficacy

In CLDK378X2101, as of the 14-April-2014 cut-off date, this Study demonstrated a high rate of rapid and durable responses with LDK378 in 246 ALK-positive NSCLC patients treated in the 750 mg dose group (the RD). LDK378 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 56.4% and 72.3% was observed in patients treated with a prior ALK inhibitor and in ALK inhibitor naïve patients respectively, by investigator assessment (Table 1-2). The median duration of response (DOR) was 8.25 months (95% CI: 6.80, 9.69) and 17.02 months (95% CI: 11.27, non-estimable) in patients treated with a prior ALK inhibitor and ALK inhibitor naïve patients respectively (Table 1-3). Median time to response was 6.1 weeks (range: 4.6 to 24.1) and 6.1 weeks (3.0 to 42.1) in patients treated with a prior ALK inhibitor and the ALK inhibitor naïve patients with confirmed complete response (CR) or PR respectively. Based on the investigator assessment 146 PFS events (123 progressions and 23 deaths) were observed with 40.7% of the patients censored. The median PFS was 6.93 months (95% CI: 5.55, 8.67) and 18.4 months (95% CI: 11.10, non-estimable) in patients treated with a prior ALK inhibitor and the ALK inhibitor naïve patients respectively (Table 1-4) (Felip et al 2014).

There were 5 patients who were previously treated with alectinib and crizotinib. LDK378 achieved confirmed PR in two, PD in one as best response and unknown in two of five patients.

[redacted]

Table 1-2 Summary of best overall response based on investigator assessment in NSCLC patients in the 750 mg dose group, by prior ALK inhibitor status (Full Analysis Set – NSCLC 750 mg) (Data cut-off: 14-April-2014)

	NSCLC with prior ALK inhibitor N=163 n (%)	NSCLC ALK inhibitor naïve N=83 n (%)
Best overall response		
Complete response (CR)	3 (1.8)	1 (1.2)
Partial response (PR)	89 (54.6)	59 (71.1)
Stable disease (SD)	29 (17.8)	14 (16.9)
Progressive disease (PD)	16 (9.8)	0
Unknown	26 (16.0)	9 (10.8)
Overall response rate (ORR) (CR or PR), n (%)	92 (56.4)	60 (72.3)
95% CI	(48.5-64.2)	(61.4-81.6)

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.

Table 1-3 Analysis of duration of response based on investigator assessment in NSCLC patients in the 750 mg dose group using Kaplan-Meier method, by prior ALK inhibitor status (Full Analysis Set – NSCLC 750 mg– Confirmed CR or PR) (Data cut-off: 14-Apr-2014)

	NSCLC with prior ALK inhibitor N=92	NSCLC ALK inhibitor naïve N=60
No. of events, n (%)	62 (67.4)	21 (35.0)
Progression	61 (66.3)	19 (31.7)
Death	1 (1.1)	2 (3.3)
No. of patients censored	30 (32.6%)	39 (65.0%)
Median DOR (month) [95%CI]	8.25 [6.80, 9.69]	17.02 [11.27, NE]

Median with 95% CI is calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

[redacted]

Table 1-4 Analysis of PFS based on investigator assessment in NSCLC patients in the 750 mg dose group, by prior ALK inhibitor status (Full Analysis Set – NSCLC 750 mg) (Data cut-off : 14-Apr-2014)

	NSCLC with prior ALK inhibitor N=163	NSCLC ALK inhibitor naïve N=83
Number of PFS events, n (%)	113 (69.3)	33 (39.8)
Progression	96 (58.9)	27 (32.5)
Death	17 (10.4)	6 (7.2)
Number of patients Censored	50 (30.7%)	50 (60.2%)
Median PFS (month) [95% CI]	6.93 [5.55, 8.67]	18.40 [11.10, NE]

Median with 95% CI is calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

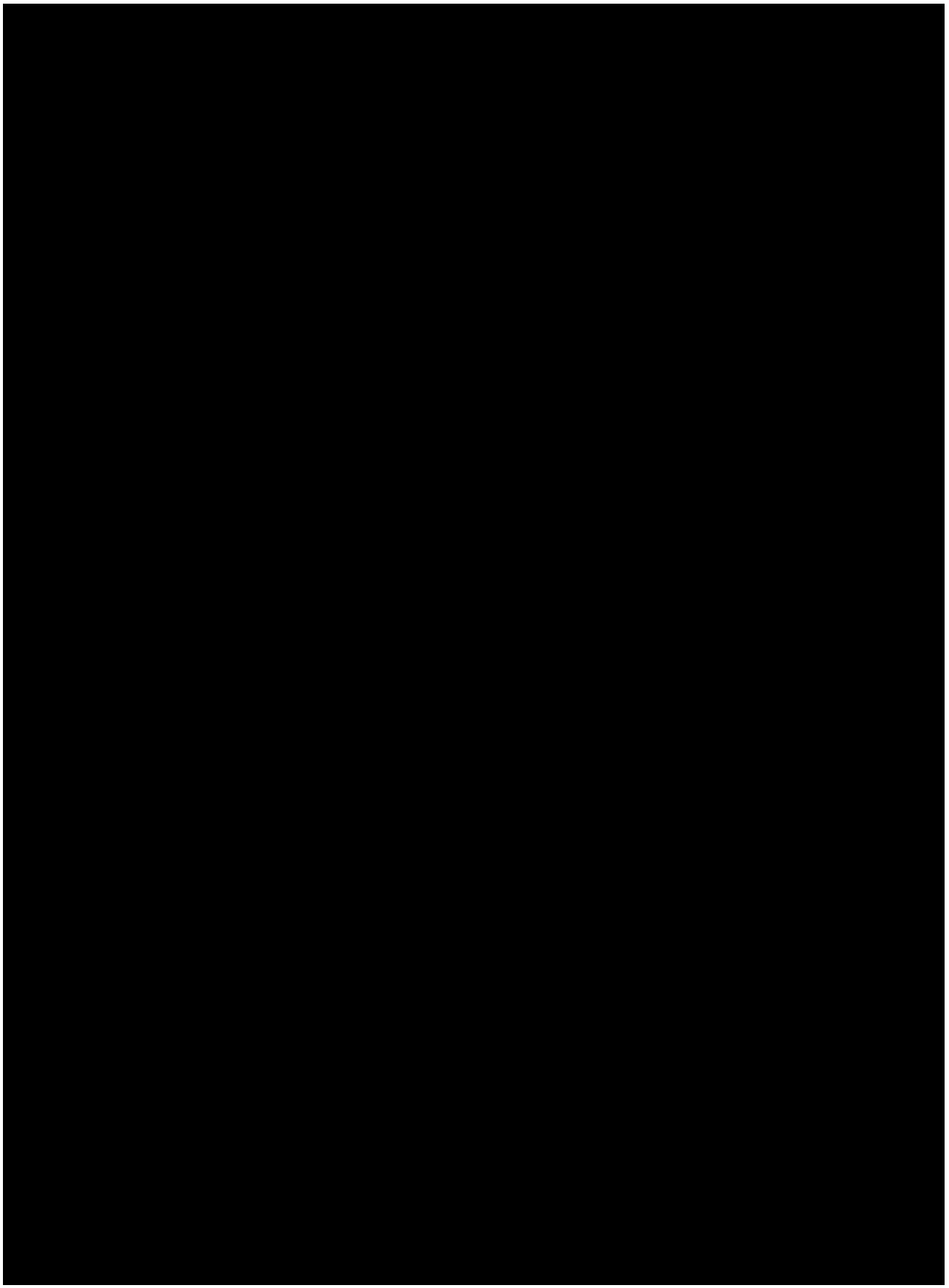
In CLDK378X1101, as of the 4-Jul-2014 cut-off date, 19 ALK positive NSCLC patients were enrolled. The majority (16/20; 80%) of patients had received prior ALK -TKI therapy. Objective responses (all PR) were documented for 10 (53%) of the 19 patients with NS CLC, with SD observed in three patients (16%), yielding a disease control rate (DCR) of 68%. Responses were observed regardless of the type of prior ALK inhibitor administered (crizotinib, alectinib or ASP3026). LDK378 achieved PR in two of the five patients pretreated with alectinib, with SD observed in a further patient. Durable clinical benefit was afforded in these three patients out of five patients resistant to alectinib, with response extending up to 10 months (Murakami et al 2014). In addition, after the above reported cut-off date, two patients who received prior alectinib were enrolled into the study. The best overall responses of two patients were SD and PR respectively. Therefore, in [CLDK378X1101] study, a total of seven patients pretreated with alectinib were enrolled and three of them achieved a PR as best overall response.

1.2.1.2.3 Clinical pharmacodynamics

Data are not available.

[redacted]

[redacted]



[redacted]

2 Rationale

2.1 Study rationale and purpose

The purpose of this phase II study is to evaluate the antitumor activity and safety profile of the novel ALK inhibitor LDK378 when used as a single agent in patients with ALK -rearranged locally advanced or metastatic NSCLC who have been pretreated with alectinib. This study is conducted in Japan.

ALK rearrangement is a relatively rare in NSCLC with a frequency of 2 -8% (Scagliotti 2012; Takeuchi 2009; Soda 2007). This rearrangement results in aberrant ALK activation. ALK fusion proteins possess potent oncogenic activity both *in vitro* and *in vivo*. This activity can be effectively blocked by small-molecule inhibitors that target ALK. Crizotinib and alectinib have been approved for ALK positive NSCLC in Japan. While crizotinib and alectinib have impressive activity in patients with ALK rearranged NSCLC, as described above, these cancers will invariably progress, with the development of resistance to crizotinib and alectinib. For these patients there is limited alternative ALK-targeted therapy. Therefore, the development of ALK TKIs with clinical activity against ALK -positive NSCLC resistant to prior ALK-TKI therapy is crucial.

LDK378 could be a therapeutic option for those who fail prior therapy with a ALK inhibitor, including alectinib. Recently, it was reported that LDK378 markedly inhibited cell proliferation of MGH056-1 cells, which was derived from a NSCLC patient who developed resistance to alectinib harboring I1171T mutation in ALK. The IC50 values of LDK378, alectinib and crizotinib were 4.3, 80 and 236 nM, respectively. In consistent with this result, treatment of this patient with LDK378 led to significant tumor regression with a confirmed partial response lasting over 7 months. In addition, LDK378 inhibited the growth of H3122 CHR-A1 NSCLC cell line, in which alectinib resistance were experimentally induced with the V1180L mutation in ALK, while alectinib and crizotinib showed less activity. These evidences suggest that LDK378 demonstrates the benefit in patients who relapsed by secondary mutations in ALK such as I1171T after treatment with alectinib (Katayama et al 2014).

In study CLDK378X2101, LDK378 has demonstrated potent antitumor activity in patients who failed crizotinib therapy mainly. Ongoing clinical phase II and III studies are investigating the activity of LDK378 in crizotinib-treated patients. The clinical experience of LDK378 in patients who failed alectinib therapy remains very limited. In study

[redacted]

CLDK378X1101, three out of seven NSCLC patients who had progressed on prior alectinib therapy and in study CLDK378X2101, two out of five NSCLC patients who had received crizotinib and alectinib therapy demonstrated a PR with durable response.

These preliminary pre-clinical and clinical data of LDK378 indicate the possibility of expanding therapeutic options for patients with ALK-rearranged NSCLC who failed prior alectinib. Alectinib was approved in Jul 2014 in Japan and it has been used widely as first line and second-line after crizotinib therapy. Additional efficacy data of LDK378 after alectinib will be clinically important.

Therefore this study will evaluate the efficacy and safety of LDK378 in patients with ALK - positive NSCLC that may have received prior crizotinib and/or up to one-line of chemotherapy, and that has progressed after alectinib therapy.

2.2 Rationale for the study design

This is a prospective, multi-center, open-label, single arm, non-randomized phase II study to evaluate the efficacy and safety of single-agent LDK378 in patients with ALK-rearranged NSCLC previously treated with alectinib. As mentioned above, clinical experien ce in this population is very limited, although a high unmet medical need exists. The target population for this study is similar to the ALK positive NSCLC population included in CLDK378X1101 and CLDK378X2101 as described above, where substantial anti-tumor activity of LDK378 has been observed.

The primary objective is to demonstrate the antitumor activity of LDK378 in this population. The primary measure of antitumor activity is the ORR according to RECIST 1.1 and will be estimated based on investigator assessment. Response rate is an appropriate primary endpoint in the context of this single arm phase II trial. A high ORR may predict clinical benefit in this rare population of patients with ALK-rearranged NSCLC that has progressed during alectinib therapy. The study will also assess DOR, DCR, time to first tumor response (TTR), progression-free survival (PFS), overall survival (OS). These endpoints are considered to be important supportive endpoints to better assess the potential clinical benefit of LDK378 in this patient population.

2.3 Rationale for dose and regimen selection

In the dose-escalation phase I study [Study CLDK378X2101], 59 patients were treated at dose levels of 50 to 750 mg. Eight Dose Limiting Toxicities (DLTs) at Cycle 1 were observed in 6 patients. Based on the Bayesian logistic regression model used to guide dose escalation, the probability of overdose (>25% probability that the DLT rate ≥ 33%) at Cycle 1 was 3.3% at the 750 mg dose level. However, during the dose-escalation discussion between the investigators and the sponsor, further dose escalation was considered to be medically inappropriate due to the increasing frequency of persistent grade 1 -2 nausea, vomiting and diarrhea, and the occasional occurrence of grade 3-4 ALT and AST increases with prolonged treatment. Further confirmation of the 750 mg dose as the appropriate MTD came from the incidence of DLTs in Cycle 1 in the first 10 patients treated at this dose in the expansion phase of the study. There were no first-cycle DLTs in these 10 patients, thus confirming the 750 mg dose as a safe MTD and RD.

[redacted]

In the dose-escalation phase I study in Japanese patients [CLDK378X1101], tolerability up to 750 mg /day was confirmed.

2.4 Rationale for choice of combination drugs

Not applicable

2.5 Rationale for choice of comparators drugs

Not applicable

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary To demonstrate the antitumor activity of LDK378, as measured by overall response rate (ORR) to LDK378 by investigator assessment per RECIST 1.1	The primary endpoints is: Overall response rate (ORR), defined as the proportion of patients with a best overall confirmed response of CR or PR in the whole body as assessed per RECIST 1.1 by the investigator.	Refer to Section 10.4.
Key secondary To evaluate response related endpoints as assessed by investigator. 1. To evaluate disease control rate (DCR) 2. To evaluate time to tumor response (TTR) 3. Duration of response (DOR)	The following endpoints will be evaluated by investigator per RECIST 1.1: 1. DCR, calculated as the proportion of patients with best overall response of CR, PR, or SD 2. TTR, calculated as the time from first dose of LDK378 to first documented response (CR or PR) for patients with confirmed CR or PR 3. DOR, calculated as the time from the date of the first documented response (CR or PR) to the first documented disease progression or death due to any cause for patients with confirmed CR or PR	Refer to Section 10.5.1.
Other secondary 1. To evaluate progression free survival (PFS) 2. To evaluate overall survival (OS) 3. To evaluate overall intracranial response rate (OIRR) 4. To evaluate the safety profile	1. PFS, calculated as the time from first dose of LDK378 to date of first documented disease progression (per RECIST 1.1) or date of death due to any cause 2. OS, calculated as the time from first dose of LDK378 to death from any cause 3. OIRR, calculated as the proportion of patients with a best overall confirmed response of CR or PR in the brain assessments for patients having measurable brain metastases at baseline 4. AEs, ECGs and laboratory abnormalities	Refer to Section 10.5.2, Section 10.5.3.

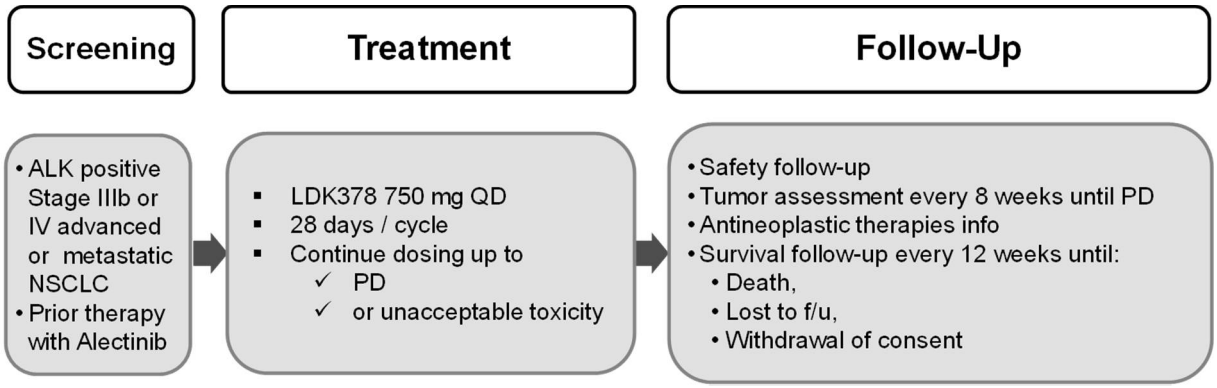
[redacted]

4 Study design

4.1 Description of study design

This is a single-arm, open-label, multicenter, phase II study to evaluate the efficacy and safety of the ALK inhibitor LDK378 when used as a single agent in patients with ALK-rearranged, stage IIIB or IV NSCLC previously treated with alectinib. A total of approximately 20 patients will be enrolled into the study. Treatment with LDK378 will continue until the patient experiences disease progression as determined by the investigator according to RECIST 1.1, unacceptable toxicity that precludes further treatment, pregnancy, start of a new anticancer therapy, discontinuation of treatment at the discretion of the patient or investigator, lost to follow-up, death, or termination of the study by Sponsor. LDK378 may be continued beyond RECIST-defined progressive disease (PD) as assessed by the investigator if, in the judgment of the investigator, there may be clinical benefit with continued treatment. In these patients, tumor assessments should continue as per the schedule of assessments until treatment with LDK378 is permanently discontinued. Patients who discontinue the study medication in the absence of progression will continue to be followed with tumor assessments until the time of PD as assessed by the investigator.

Figure 4-1 Study design



4.1.1 Screening

All patients must sign an Informed Consent Form (ICF) prior to any screening procedures and prior to determination of eligibility criteria.

Patients must have been treated with Alectinib. With respect to the chemotherapy, patients must be chemotherapy-naïve or have received 1 lines of prior cytotoxic chemotherapy to treat their stage IIIb or IV NSCLC. Patients must have been treated with the alectinib treatment andprior therapy with crizotinib as ALK inhibitor therapy in addition to alectinib is allowed. Alectinib doesn't need to be the last therapy prior to study enrollment. No particular sequence of prior alectinib and crizotinib is required for enrollment.

Eligibility assessment will be conducted within 28 days prior to starting the study drug. Approximately 20 patients will be enrolled.

[redacted]

4.1.2 Treatment duration

The treatment period begins on Day 1 of Cycle 1. All patients will be treated with LDK378, administered orally, at a starting dose of 750 mg.

Treatment with LDK378 will continue until the patient experiences disease progression as determined by the investigator according to RECIST 1.1, unacceptable toxicity that precludes further treatment, pregnancy, start of a new anticancer therapy, discontinuation of treatment at the discretion of the patient or investigator, lost to follow-up, death or termination of the study by Sponsor.

4.1.2.1 Tumor assessments during study conduct

Tumor response will be evaluated starting from the first day of treatment with LDK378, every 8 weeks, until the time of disease progression according to RECIST 1.1 as determined by investigator, withdrawal of consent for further follow-up, loss to follow-up or death. This schedule of tumor assessment must continue regardless of dose interruptions.

4.1.2.2 End of Treatment (EOT)

When the patient discontinues from study treatment, End of Treatment (EOT) visit must be performed as soon as possible and within 7 days of the last dose of LDK378. Patients will be contacted for the safety follow-up 30 days after their last dose of LDK378 to determine if they have experienced any new AEs and/or to follow resolution of ongoing AEs.

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

4.1.3 Follow-up period

Safety follow-up

All patients will be followed for AEs and SAEs for at least 30 days following the last dose of study treatment at the end of treatment phase.

Post-treatment follow-up

All patients who discontinued treatment during the treatment phase for reasons other than death, lost to follow-up, pregnancy or PD (radiological as assessed by investigator) (Section 7.1.3) will continue tumor assessments thereafter until PD (radiological as assessed by investigator), or withdrawal of consent or death.

Survival follow-up

All patients who had PD as per investigator assessment and/or withdrew consent from further study assessments will subsequently be followed for survival information every 3 months until death, lost to follow-up or withdrawal of consent for survival follow-up.

[redacted]

4.2 Timing of interim analyses and design adaptations

There are no interim analyses and design adaptations planned in this study.

4.3 Definition of end of the study

There will be no interim analysis of efficacy. The primary analysis will occur once all patients have completed at least 6 cycles of treatment with LDK378 or have discontinued earlier. Following the primary analysis time point, the study will remain open. Patients still being followed on the study will continue as per the schedule of assessments.

The study will end once at least approximately 75% of patients have died or are lost to follow-up. The final analysis of study data will be conducted at the end of the study. All available data from all patients up to this cutoff date will be analyzed. These data will be summarized in the Clinical Study Report (CSR).

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

This study will be conducted in adult male or female patients, with ALK-rearranged (as determined by Vysis ALK Break Apart FISH Probe kit [Abbott Molecular Inc.]), advanced (stage IIIB or IV) NSCLC who have progressed since prior therapy with alectinib. Prior crizotinib and/or one regimen or less of cytotoxic chemotherapy are allowed.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies while on treatment. Patients must meet the eligibility criteria outlined in Section 5.2 and Section 5.3 to be enrolled in this study. Rescreening of patients during the screening period will not be allowed, but laboratory parameters may be retested within the 28-day screening period for an individual patient if such parameters meet an exclusion criterion when initially tested.

5.2 Inclusion criteria

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

1. Histologically or cytologically confirmed diagnosis of NSCLC that carries an ALK rearrangement as determined locally by Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test. If documentation of ALK rearrangement is not available as described

[redacted]

above, a test to confirm ALK rearrangement must be performed locally by Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) prior to study. It is preferable to use a new tumor biopsy obtained prior to the first LDK378 dose or, if not available, in archival tumor obtained at or since the time of diagnosis.

2. Stage IIIb or IV NSCLC
3. At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.

4a Patients must have NSCLC that has progressed at study enrollment.

5a Patients must have received previous treatment with alectinib for treatment of locally advanced or metastatic NSCLC. Prior therapy with crizotinib as ALK inhibitor therapy in addition to alectinib is allowed. Alectinib doesn't need to be the last therapy prior to study enrollment. No particular sequence of prior alectinib and crizotinib is required for enrollment.

- A minimum of 21 days of treatment with alectinib will be required to qualify as one prior course of alectinib (unless alectinib was discontinued due to PD after a shorter treatment course).
- Patients may have discontinued alectinib therapy for disease progression, intolerance or other reason.

6. Patients must be chemotherapy-naïve or have received only one line of prior cytotoxic chemotherapy. If patients received chemotherapy, such patients must have progressed during or after the last chemotherapy regimen received prior to the first dose of LDK378.
   - Prior therapy with bevacizumab will be allowed if it was a component of the previous platinum-based regimen.
   - Prior maintenance therapy (e.g., bevacizumab, pemetrexed) will be allowed if it was a component of the previous platinum-based regimen.
   - For chemotherapy regimens given every 21 or 28 days, Minimum of two cycles will be required to qualify as a prior chemotherapy regimen (unless chemotherapy was discontinued due to progressive disease after one cycle). If chemotherapy were discontinued for a reason other than disease progression after only one cycle, then this regimen does not count as a prior line of chemotherapy.
   - Neoadjuvant or adjuvant cytotoxic chemotherapy will count as one prior treatment regimen, if relapse occurred within 12 months from the end of the neoadjuvant or adjuvant cytotoxic chemotherapy, respectively.
7. Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v 4.03). Patients with grade ≤ 2 peripheral neuropathy or any grade of alopecia, fatigue, nail changes or skin changes are allowed to enter the study.
8. Age 18 years or older at the time of informed consent.
9. Patients must have a tumor tissue sample available, as an archival sample (collected either at the time of diagnosis of NSCLC or any time since) [redacted]
10. Patients must meet the following laboratory values at the screening visit:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

[redacted]

- Platelets ≥ 75 x 10^9/L
- Hemoglobin ≥ 8 g/dL
- Serum creatinine <1.5 mg/dL
- Total bilirubin ≤ 1.5 x ULN (Upper limit of normal), except for patients with Gilbert's syndrome, who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN
- Aspartate transaminase (AST) ≤ 3 x ULN, except for patients with liver metastasis, who are only included if AST ≤ 5 x ULN
- Alanine transaminase (ALT) ≤ 3 x ULN, except for patients with liver metastasis, who are only included if ALT ≤5 x ULN
- Alkaline phosphatase (ALP) ≤ 5 x ULN
- Serum amylase ≤ 2 x ULN
- Serum lipase ≤ ULN
- Fasting plasma glucose ≤ 175 mg/dL (≤ 9.8 mmol/L)

11. Patients must have the following laboratory values within the laboratory normal limits or corrected to within normal limits with supplements before the first dose of LDK378
    - Potassium
    - Magnesium
    - Phosphorus
    - Total calcium (corrected for serum albumin)

12a. World Health Organization (WHO) performance status 0-1.

13. Written informed consent must be obtained prior to any screening procedures. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.

14. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.

5.3 Exclusion criteria

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

1. Patients with known hypersensitivity to any of the excipients of LDK378 (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate).
2. History of carcinomatous meningitis.

3a Prior therapy with other ALK inhibitor investigational agents except crizotinib and alectinib.

4a Prior systemic anti-cancer (including investigational) therapy aside from alectinib, crizotinib and one regimen of previous cytotoxic chemotherapy for locally advanced or metastatic NSCLC.

5. Patients with symptomatic CNS metastases who is neurologically unstable or has required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms.

[redacted]

6. 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).
7. Patient who has received thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs) radiotherapy ≤ 2 weeks prior to starting the study treatment or has not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to the first dose of study drug is allowed.
8. Patient has had major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to the first dose of study drug or has not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can receive study treatment ≥1 week after the procedure.
9. Patient with a concurrent malignancy or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma *in situ* of any type.
10. Patient has a history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.
11. Patient has clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months), such as:
    - Unstable angina within 6 months prior to screening.
    - Myocardial infarction within 6 months prior to screening.
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV).
    - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to screening.
    - Ventricular arrhythmias.
    - Supraventricular and nodal arrhythmias not controlled with medication.
    - Other cardiac arrhythmia not controlled with medication.
    - Corrected QT (QTcF) > 470 msec using Fridericia's correction on the screening ECG (as mean of triplicate ECGs).
12. Patient receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with LDK378 and for the duration of the study (Appendix 1):
    - Strong inhibitors or strong inducers of CYP3A4/5.
    - Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5 and/or CYP2C9.

- Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes.

13. Patient has impairment of GI function or GI disease that may significantly alter the absorption of LDK378 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
14. Patient is currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants.
15. Patient is 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. Note: Dose of steroids must be stable for 5 days before the baseline brain MRI.
16. Patient is receiving treatment with any enzyme-inducing anticonvulsant (Appendix 1) that cannot be discontinued at least 1 week before first dose of study treatment, and for the duration of the study. Patients on non enzyme-inducing anticonvulsants are eligible.
17. Patient is pregnant or nursing (lactating) woman, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
18. Patient is a woman of child-bearing potential, defined as a woman physiologically capable of becoming pregnant, **unless** they are using highly effective contraception during dosing and for 3 months after stopping LDK378 treatment.
    Highly effective contraception is defined as any of:
    - Total abstinence: when this is in line with the preferred and usual lifestyle of the patient. [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 partner sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient.
    - 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.

    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 have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

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

6 Treatment

6.1 Study treatment

For this study, the term "investigational" refers to LDK378. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

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

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

6.1.1 Dosing regimen

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

Each study site will be supplied with LDK378 by Novartis. LDK378 is supplied as 150 mg hard gelatin capsules as individual patient supply, packaged in bottles. Medication labels will comply with legal regulation and be printed in local language. The storage conditions for the study treatment will be described on the medication label. LDK378 will be dispensed by the pharmacist or designee at the investigator's institution.

LDK378 will be administered orally once daily at a dose of 750 mg (five 150 mg capsules) on a continuous dosing schedule. The investigator must instruct the patient to take the study drug exactly as prescribed.

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

- Patients should take LDK378 once daily at approximately the same time each day in the morning, afternoon, or evening.
- Patients should take LDK378 on an empty stomach (i.e. fast from food and drink, except water) at least 1 hour before or 2 hours after a light meal. Each dose of LDK378 should be taken with a glass of water and consumed over as short a time as possible (i.e. not slower than 1 capsule every 2 minutes).
- Patients should be instructed to swallow whole capsules and not to chew or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

[redacted]

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

Table 6-1 Dose and treatment schedule

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

[redacted]

6.1.2 Guidelines for continuation of treatment

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

6.1.3 Treatment duration

Patients will continue LDK378 until they experience any of the following:

- Disease progression (radiologically documented according to RECIST 1.1 by the investigator). LDK378 therapy will continue until progressive disease if clinically acceptable. However, LDK378 may be continued beyond RECIST-defined progressive disease (PD) as assessed by the investigator, if in the judgment of the investigator, there may be clinical benefit with continued treatment.
- Unacceptable toxicity that precludes further treatment
- Start of a new anti-cancer therapy
- Pregnancy
- Treatment is discontinued at the discretion of the investigator or patient
- Lost to follow-up
- Death
- Study terminated by Sponsor

Patients who permanently discontinue the study drug for any reason other than disease progression must, if agreeing to further follow-up, continue efficacy assessments as scheduled in the protocol until the time of confirmed disease progression.

6.1.4 Definition of treatment cycle

A treatment cycle is defined as 28 calendar days from the start of treatment with LDK378 (Day 1, Cycle 1) for the purposes of scheduling procedures and evaluations.

6.2 Dose escalation guidelines

Not applicable to this study

[redacted]

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patients to continue the study treatment. Any changes in LDK378 must be recorded on the Dosage Administration Record eCRF.

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

For grade 1 and tolerable grade 2 treatment-related toxicities, patients 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 and after discussion with the Sponsor. For any grade 3 or 4 treatment-related toxicity that is considered by the investigator to be life-threatening, permanently discontinue study treatment.

More detailed LDK378 modification guidelines are described in Section 6.3.3 and Table 6-3 selected toxicities.

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE) version 4.03. Patients whose treatment is interrupted or permanently discontinued due to an AE must be followed until resolution or stabilization of the event. Patients requiring interruptions greater than 28 consecutive days will be discontinued from study treatment. In certain cases, if the Investigator and the Sponsor conclude that a patient, who has experienced a treatment interruption greater than 28 consecutive days, could benefit from additional treatment, continuation may be allowed.

6.3.2 Treatment interruption and treatment discontinuation

If the administration of LDK378 is temporarily interrupted for reasons other than toxicity, then treatment with LDK378 may be resumed at the same dose. The same applies if the patient experiences an unacceptable toxicity not specifically described in Table 6-3, provided this toxicity resolved to ≤ CTCAE grade 1.

If the treatment with LDK378 is withheld due to toxicity, scheduled visits and all assessments should continue to be performed (with the exception of the dosing of the withheld study drug), as described in Table 7-1.

If the treatment with LDK378 dosing is withheld for more than 28 consecutive days consecutive days (counting from the first day when a dose was missed), due to treatment-related toxicity, then LDK378 should be permanently discontinued except in cases where the investigator believes the patient continues to derive clinical benefit. In such cases, treatment with LDK378 may be resumed at a lower dose.

[redacted]

Detailed guidelines for follow-up of study drug related AE or an abnormal laboratory value 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 LDK378. Patients whose treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

6.3.3 Criteria for LDK378 dose modifications

LDK378 dose reduction will follow the dose reduction steps described in Table 6-2. For each patient, a maximum of 3 dose modifications is allowed after which the patient must be discontinued from treatment with LDK378. Once the dose of LDK378 has been reduced, it cannot be re-escalated. If a patient continues treatment with LDK378 after RECIST-defined PD as determined by the investigator, the criteria for dose modification will also apply.

Table 6-2 Dose reduction steps for LDK378

LDK378 dose levels	Dose* and schedule
Starting dose level	750 mg qd continuously
Dose level – 1	600 mg qd continuously
Dose level – 2	450 mg qd continuously
Dose level – 3	300 mg qd continuously **

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

**Dose reduction below 300 mg/day is not allowed. If a dose reduction below 300 mg/day is required, the patient should be permanently discontinued from LDK378

Guidelines for dose interruptions and re-initiation of LDK378 treatment (with or without dose reduction) are described in Table 6-3.

[redacted]

Table 6-3 Criteria for interruption and re-initiation of LDK378 treatment

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
HEMATOLOGICAL	
Neutropenia (ANC: Absolute neutrophil count)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 and ≥ 1.0 x 10^9/L) Grade 3 (ANC < 1.0 and ≥0.5 x 10^9/L)	Maintain dose level
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a **single** temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until clinically resolved and neutropenia ≤ Grade 2, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 and ≥ 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50 and ≥ 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level
HEPATIC	
Alkaline phosphatase and/or Gamma-glutamyl transpeptidase (**GGT**)	
Isolated elevations of any grade	Maintain dose level
Total Bilirubin (for patients with Gilbert Syndrome these dose modifications apply to changes in direct [conjugated] bilirubin only)	
Grade 1 (> ULN and ≤ 1.5 x ULN)	Maintain dose level with liver function test (LFTs)*** monitored as per protocol

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
Grade 2 (> 1.5 and ≤ 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 and ≤ 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days discontinue patient from LDK378
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from LDK378
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, 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, then ↓ 1 dose level
AST or ALT and concurrent total bilirubin	
AST or ALT > 3.0 x ULN with total bilirubin > 2.0 x ULN in the absence of cholestasis or hemolysis	Permanently discontinue patient from LDK378 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 LDK378 for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
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 x baseline; >1.5 and ≤3.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 x baseline ; >3.0 and ≤6.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from LDK378
GASTROINTESTINAL	
Diarrhea**	
Grade 1	Maintain dose level but adjust anti-diarrhea treatment
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then maintain dose level. If diarrhea returns as ≥ Grade 2, then omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 3 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Nausea***	
Grade 1 or 2	Maintain dose level but adjust anti-emetic treatment
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Vomiting***	
Grade 1	Maintain dose level but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then maintain dose level. If vomiting returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then ↓ 1 dose level.
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
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 LDK378 at ↓ 1 dose level If adequate hyperglycemic control cannot be achieved with optimal medical management permanently discontinue patient from LDK378
GENERAL DISORDERS	
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	If grade 3 fatigue resolves to Grade 2 in ≤ 7 days, maintain dose level If grade 3 fatigue lasts > 7 days, omit dose until resolved to ≤ Grade 2 and then ↓ dose level
PULMONARY	
Notes: • Withhold LDK378 for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD. • During evaluation of potential grade 2, 3, and 4 pneumonitis, if an infectious etiology is confirmed (i.e., pneumonia) and pneumonitis is excluded, then consider resuming LDK378 at current dose level after the pneumonia resolves.	
PNEUMONITIS	
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue patient from LDK378
CARDIAC	
Electrocardiogram QT corrected (QTcF) interval prolonged	
Grade 1 (QTcF 450-480 ms) Grade 2 (QTcF 481-500 ms)	Maintain dose level

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
Grade 3 (QTcF ≥ 501 ms on at least two separate ECGs)	Omit dose until QTc is less than < 481 ms, then ↓ 1 dose level - Assess the quality of the ECG recording and the QT value and repeat if needed - Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTc < 481 ms In addition:-Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment - Review concomitant medication use for drugs with the potential to increase the risk of drug exposure related to QT prolongation After resumption of dosing: - Repeat ECGs 7 days after dose resumption for all patients who had therapy interrupted due to QTc ≥ 501 ms.
Grade 4 (QTcF ≥ 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 LDK378
BRADYCARDIA	
Grade 1 or Grade 2	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm Evaluate concomitant medications known to cause bradycardia and adjust the dose of LDK378
Grade 3 Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm If the concomitant medication can be adjusted or discontinued, resume LDK378 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 patient from LDK378

Worst toxicity (CTCAE 4.03 Grade)*	Dose Modifications for LDK378
* Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All dose modifications should be based on the worst preceding toxicity. ** If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g.,review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the Investigator. ***LFTs include albumin, ALT, AST, total bilirubin, alkaline phosphatase and GGT. **** Dose modifications apply to patients who experience diarrhea despite appropriate antidiarrheal medication. This medication should be started at the first sign of abdominal cramping, loose stools or overt diarrhea (see Section 6.3.4.6). ***** Dose modifications apply to patients who experience nausea and/or vomiting despite appropriate antiemetic medication. This medication should be started at the first sign of nausea and/or vomiting (see Section 6.3.4.5).	

[redacted]

6.3.4 Follow-up for toxicities

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

6.3.4.1 Guidelines for the follow-up of laboratory hematologic abnormalities

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

6.3.4.2 Guidelines for the follow-up of liver laboratory abnormalities

In patients with any clinically relevant laboratory liver abnormality, as defined below, hepatic toxicity monitoring must include **ALL** of the following live 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 4weeks. For patients with liver metastasis and grade 2 AST/ALT at baseline, increased monitoring is required for grade 3/4 AST/ALT; follow guidelines for grade 3 or 4 AST/ALT.

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

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

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

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

- 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, creatinine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
  - A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
  - Further testing for acute hepatitis A, B, C or E infection and liver imaging (eg, biliary tract) may be warranted.
  - Blood sample can be collected as close as possible to last dose of study drug in the event that a patient experiences hepatotoxicity, as needed.
  - Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

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

6.3.4.3 Guidelines for the follow-up of renal laboratory abnormalities

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

[redacted]

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

Monitor patients for pulmonary symptoms indicative of pneumonitis. In addition, withhold LDK378 for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD.

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

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

Nausea and vomiting are among the most frequently reported AEs following treatment with LDK378 and patients must therefore be closely monitored for the appearance of these AEs.

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

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

Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator's best judgment. For moderate emetogenic drugs, such as LDK378, International Guidelines for anti-emetic treatment recommend early treatment with 5-HT3-receptor antagonists (5-HT3RAs).

Dose adaptation of LDK378 in case of treatment related nausea and/or vomiting must follow the guidelines presented above in Table 6-3.

6.3.4.6 Guidelines for the treatment of study drug induced diarrhea

Diarrhea is among the most frequently reported AEs following treatment with LDK378, and patients must therefore be closely monitored for the appearance of this AE.

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

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

[redacted]

- 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 intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg SC tid or 25 to 50 µg IV) and antibiotics (e.g. fluoroquinolone) should be given.

Dose adaptation of LDK378 in case of treatment related diarrhea 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 LDK378 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 LDK378 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 LDK378. For any grade of hypophosphatemia during the study, treatment with phosphate supplements should be given as clinically indicated, and the LDK378 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 (i.e. 4 weeks). If there is no recurrence of ≥ grade 2 amylase or lipase elevations during this period, subsequent monitoring must be performed every 4 weeks.

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

If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, withhold LDK378, 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.

[redacted]

Table 6-4 Follow-up evaluations for selected toxicities

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

6.3.5 Anticipated risks and safety concerns of the study treatment

Appropriate eligibility criteria and specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, e.g., diarrhea are provided in Section 6.3.4. Refer to preclinical toxicity and or clinical data found in the Investigator's brochure (IB).

6.4 Concomitant medications

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

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications including herbal/natural medications (excluding study treatment and prior antineoplastic treatments and blood transfusions), surgeries and procedures (including physical therapy) administered within 28 days prior to the

[redacted]

first dose of administration of LDK378 through 30 days after the last dose of LDK378 will be recorded in the Concomitant Medications or Surgical and Medical Procedures eCRF, respectively. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications (prohibited, see Section 6.4.2.7), food and or vitamin supplements.

6.4.1 Permitted concomitant therapy

6.4.1.1 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to induce CYP3A enzymes, thereby increasing the risk of reducing LDK378 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 or prednisone (e.g., for tumor associated symptoms) are permitted during the course of the study. If increasing doses of corticosteroids are required during the study treatment, LDK378 must be held and the corticosteroid dose must have been stabilized (or decreasing) for at least 5 days before LDK378 is resumed.

6.4.1.2 Bisphosphonates

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

No drug-drug interaction is expected between LDK378 and bisphosphonates as the two drugs are eliminated through different elimination pathways. Bisphosphonates are not inhibitors of human CYP450 enzymes involved in the metabolism of LDK378 and do not undergo metabolism in vivo.

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

6.4.1.3 Drugs that are metabolized by CYP450 enzymes

In vitro drug metabolism studies show that the metabolism of LDK378 is mediated by CYP3A4/5. LDK378 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 LDK378 on substrate drugs metabolized by these enzymes in patients. The risk for CYP2A6 and CYP2E1 is largely mitigated by the low potential for drugs metabolized by these enzymes to be co-administered with LDK378.

[redacted]

Concomitant treatment of LDK378 with weak inhibitors or inducers of CYP3A4/5 is permitted. Caution is advised when LDK378 is co-administered with drugs that are moderate inhibitors or inducers of CYP3A4/5 (Table 14-2 of Appendix 1). Duration of concomitant treatment should be kept as short as possible (e.g., less than 1 week), or completely avoided whenever possible. Patients receiving such medications must be monitored closely for any potentiation 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 LDK378 with strong inhibitors and inducers of CYP3A4/5 is prohibited (refer to Section 6.4.2.5).

Concomitant treatment of LDK378 with medications known to be metabolized by CYP2C9 and CYP3A4is allowed with caution (Table 14-2 of Appendix 1), except for drugs which have narrow therapeutic index/sensitive substrates for these CYP isoforms (Section 6.4.2.6 and Table 14-1 of Appendix 1).

6.4.1.4 Non-enzyme inducing anti-epileptic drugs

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

6.4.1.5 Palliative radiotherapy and surgery

Local radiotherapy for isolated brain progression, 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 study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be assessed and documented.

Patients who develop progressive disease but are still deriving clinical benefit from LDK378 therapy, as determined by the Investigator may undergo radiotherapy and/or surgical resection as palliative localized therapy to treat metastatic lesions. LDK378 should be held for at least 4 days prior to radiotherapy and at least 1 day prior to any surgery. LDK378 may be resumed ≥3 days after completing radiotherapy or minor surgery, and ≥2 weeks after major surgery.

6.4.1.6 Gastric protection agents

The use of gastric protection agents including antacids, H2-antagonists, and proton pump inhibitors (PPIs) is allowed Table 14-2 of Appendix 1). However, PPIs should be used with caution due to the theoretical effects of long-acting pH elevating agents (i.e., prolonged acid suppression) on reducing LDK378 absorption. When the concurrent use of a H2-antagonist or an antacid with LDK378 is necessary, the H2 blocker must be administered 10 hours before or 2 hours after the LDK378 dose, and the antacid must be administered 2 hours before or 2 hours after the LDK378 dose. Time restrictions for the concurrent use of PPIs and LDK378 are not applicable due to the long-acting effects of PPIs on gastric pH (i.e., separation of doses will not likely impact this interaction).

6.4.2 Prohibited concomitant therapy

6.4.2.1 Other anticancer therapy

Anticancer therapy (chemotherapy, targeted therapy, biologic therapy or radiation therapy [except palliative radiotherapy as described in Section 6.4.1.5], anti-cancer surgery and

[redacted]

immunotherapy) other than the study treatment must not be given to patients while they are enrolled in the treatment portion of the trial. If such agents are required then the patient must be permanently discontinued from the treatment portion of the study.

6.4.2.2 Other investigational therapies

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

6.4.2.3 Warfarin and coumarin derivatives

Warfarin sodium or any other coumarin-derivative anticoagulant are not permitted. LDK378 is an inhibitor of CYP2C9, the major metabolizing enzyme of warfarin. A clinically relevant increase in warfarin exposure is possible.

6.4.2.4 Enzyme inducing anti-epileptic drug

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

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

If a patient was previously on a non-EIAED and needs to permanently change anticonvulsant agent but cannot change to another non-EIAED, the patient will be taken off LDK378.

6.4.2.5 Strong CYP3A inhibitors and inducers

In vitro metabolism studies suggest that oxidative metabolism of LDK378 is predominantly mediated by CYP3A4/5.

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

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

LDK378 is a potent inhibitor of drugs metabolized by 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 LDK378. Refer to Table 14-1 of Appendix 1 for a list of these medications. Please note that this list may not be comprehensive.

6.4.2.7 Herbal medications

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

[redacted]

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

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

LDK378 has potent activity on the hERG channel with an IC_{50} of 0.4 μM. However there were no LDK378-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 LDK378 on the QT interval in an open-label, dose-escalation, and expansion study ([CLDK378X2101]). A total of 304 patients were treated with LDK 378 doses ranging from 50 to 750 mg with 255 patients treated with LDK378 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 LDK378 750 mg. A pharmacokinetic/pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation.

Concomitant administration of LDK378 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 LDK378 and any medication included in Table 14-4 of Appendix 1 titled "List of prohibited QT prolonging drugs" (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a known risk of causing Torsades de Pointes) is not permitted.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. Once assigned, the Patient No. must not be reused for any other patient and the Subject No.

6.5.2 Treatment assignment

Not applicable since this study consists of a single arm and no randomization.

6.5.3 Treatment blinding

Not applicable

[redacted]

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.

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

6.6.1 Study drug packaging and labeling

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

6.6.2 Drug supply and storage

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

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

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

Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of LDK378 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 LDK378 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

[redacted]

completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

Not applicable

6.6.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X" the visits when they are performed. Each treatment cycle is 28 days (the 28 days cycle length is fixed regardless of whether the dose of LDK378 is withheld). All visits are to be scheduled according to the appropriate number of calendar days from Cycle 1 Day 1 of study drug administration. A visit window of +/- 1 day in Cycle 1 and +/- 3 days in Cycle 2 onwards is allowed. Imaging evaluations may be performed +/-7 days of the due date of the assessment.

Note: If treatment with LDK378 is withheld at any time during the study, all study visits, safety and efficacy assessments should continue according to the appropriate number of calendar days from Cycle 1 Day 1 as per the schedule of assessments.

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

[redacted]

Table 7-1 Visit evaluation schedule

				Treatment Phase				Post treatment follow up phase			Survival follow-up phase
		Protocol Section	Screening Phase	Cycle 1 (28 d)		Subsequent cycles (28 d)	End of study Treatment (EOT)				
Visit name	**Category**		**Screening Visit (Day -28 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Day 1**	**End of treatment visit**	**30-day safety follow-up**	**Tumor follow- up if no PD at the EOT**	**Study phase completion**	**Survival follow-up**
Obtain Main Informed Consent	D	7.1.1.	X								
Collection of documentation of ALK rearrangement OR confirmation of ALK status	D	7.1.1.3.	Archival tissue and/or new biopsy & pathology report								
End of Phase Disposition Page	D	7.1.3.	X Screening Phase Disposition (eCRF)				X End of Treatment Phase Completion (eCRF)			X End of post treatment phase disposition	
Demography	D	7.1.1.3.	X								
Inclusion/ exclusion criteria	D	5.2, 5.3.	X								
Eligibility check	S	7.1.1.1.	X								
Relevant medical history/current medical conditions	D	7.1.1.3.	X								
Smoking history	D	7.1.1.3.	X								
Diagnosis and extent of cancer	D	7.1.1.3.	X								
Prior antineoplastic therapies (meds, surgery, radiation)	D	7.1.1.3.	X								
Prior and concomitant medications	D	7.1.1.3.	X	Continuous							
Physical examination	S	7.2.2.1.	X	X	X	X	X				
Performance status (WHO)	D	7.2.2.4.	X	X		X	X				
Height	D	7.2.2.3.	X								

[redacted]

	Category	Protocol Section	Screening Phase	Treatment Phase				Post treatment follow up phase			Survival follow-up phase
				Cycle 1 (28 d)		Subsequent cycles (28 d)	End of study Treatment (EOT)				
Visit name			**Screening Visit (Day -28 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Day 1**	**End of treatment visit**	**30-day safety follow-up**	**Tumor follow- up if no PD at the EOT**	**Study phase completion**	**Survival follow-up**
Weight	D	7.2.2.3.	X	X		X	X				
Vital signs	D	7.2.2.2.	X	X	X	X	X				
Hematology	D	7.2.2.5.1.	X	X	X	X	X				
Blood chemistry	D	7.2.2.5.2.	X	X	X	X	X				
Urinalysis (dipstick) with micro-analysis	D	7.2.2.5.3.	X								
Serum Pregnancy test	D	7.2.2.5.4.	X								
Urine Pregnancy test (Prior to dosing)	D	7.2.2.5.4.		X		X	X				
Testosterone, LH, FSH	D	7.2.2.5.5.	X	X	X	X	X				
Coagulation	D	7.2.2.5.6.	X								
ECG	D	7.2.2.6.1.	X	X	X	X	X				
CT scan or MRI of chest and abdomen	D	7.2.1.	X			X Cycle 3 then every 2nd cycle (i.e. every 8 weeks)	X		X Every 8 weeks following EOT until PD if no PD at the EOT		
Whole body bone scan	D	7.2.1.	X	If clinically indicated							

[redacted]

	Category	Protocol Section	Screening Phase	Treatment Phase				Post treatment follow up phase			Survival follow-up phase
				Cycle 1 (28 d)		Subsequent cycles (28 d)	End of study Treatment (EOT)				
Visit name			**Screening Visit (Day -28 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Day 1**	**End of treatment visit**	**30-day safety follow-up**	**Tumor follow- up if no PD at the EOT**	**Study phase completion**	**Survival follow-up**
CT scan or MRI of brain	D	7.2.1.	X			X Cycle 3 then every 2nd cycle (i.e. every 8 weeks): only if clinically indicated or positive at baseline	X Only if clinically indicated or positive at baseline		X Every 8 weeks following EOT until PD (only if clinically indicated or positive at baseline)		
• CT scan or MRI of other metastatic sites (e.g. neck, pelvis, etc) • Localized bone CT scan, MRI or x-ray (for any lesions identified on the whole body bone scan that are not visible on the chest/abdomen CT scan or MRI) • Photography (for any skin lesions)	D	7.2.1.	X (if clinically indicated)			X Cycle 3 then every 2 cycle (i.e. every 8 weeks): only if positive at baseline or clinically indicated	X Only if positive at baseline or clinically indicated		X Every 8 weeks following EOT until PD (only if positive at baseline or clinically indicated)		
LDK378 dosing	D	6.1.1.		Continuous							
Adverse events	D	8.1.	Continuous								

[redacted]

	Category	Protocol Section	Screening Phase	Treatment Phase				Post treatment follow up phase			Survival follow-up phase
				Cycle 1 (28 d)		Subsequent cycles (28 d)	End of study Treatment (EOT)				
Visit name			**Screening Visit (Day -28 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Day 1**	**End of treatment visit**	**30-day safety follow-up**	**Tumor follow- up if no PD at the EOT**	**Study phase completion**	**Survival follow-up**
[redacted]											
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5.3.						X	X		X Every 12 weeks
Survival assessment	D	7.1.5.3.									X Every 12 weeks

[redacted]

7.1.1 Screening

Written informed consent must be obtained before any study specific procedure is performed. Screening assessments to confirm eligibility into the main study should be performed as per the schedule of assessments. Re-screening of patients will not be allowed, but laboratory parameters which do not meet the inclusion criteria may be re-tested within the screening window (Day -28 to Day -1).

7.1.1.1 Eligibility screening

After the patient has signed the consent form to participate in the study, a registration sheet will be completed and faxed or emailed to the Novartis for approval and acknowledgement of entry of the patient onto the study. Details on the enrollment process are provided to investigators as the instruction.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screening failure.

The following eCRFs must be completed for screening failure patients:

- Screening Phase Disposition page (including reason for not being started on treatment)
- Informed consent
- Demography
- Adverse Events (only if an SAE occurs)
- Inclusion/Exclusion criteria
- Death
- Withdrawal of consent

7.1.1.3 Patient demographics and other baseline characteristics

Data to be collected on patient characteristics at screening include:

- Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)
- Relevant medical history
- History of smoking
- NSCLC diagnosis and extent of disease, including:
  - Date of diagnosis of NSCLC
  - ALK status documentation using the Vysis ALK break-apart FISH assay. If such documentation is not available, ALK status must be confirmed using the Vysis ALK break-apart FISH test in site locally (preferably using a new tumor biopsy obtained prior to the first LDK378 dose or, if not available, in archival tumor obtained at or since the time of diagnosis) prior to study entry.
  - Site of active disease
  - Characteristics of disease

[redacted]

- Concomitant molecular alteration when available (and results of all the tests performed even if wild type)
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and Concomitant Medications, surgical and medical procedures
- Neurological examination and use of steroids to control CNS symptoms (only for patients with symptomatic CNS metastases)

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

7.1.2 Treatment period

The study treatment phase begins on Cycle 1, Day 1 with the first administration of LDK378 and will continue until unacceptable toxicity that precludes further treatment, start of a new anti-cancer therapy, treatment is discontinued at the discretion of the investigator and/or patient death. If a patient experiences disease progression (radiologically documented according to RECIST 1.1 as assessed by the investigator), LDK378 administration may be stopped, or may be continued if the patient is continuing to derive clinical benefit in the opinion of the investigator.

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

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

7.1.3 Discontinuation of study treatment

A patient will be defined as on the study if they are continuing to have any study data collected, i.e. if the patient is being treated with LDK378, is in efficacy follow-up after discontinuing LDK378, or is in survival follow-up.

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

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

Study treatment must be discontinued under the following circumstances:

- Emergence of adverse events, as described in Section 6.3.
- Laboratory abnormalities, as described in Section 6.3.
- Pregnancy
- Deviations from the prescribed dose regimen, as described in Section 6.1.1.

- Use of prohibited treatment, as described in Appendix 1 for LDK378
- Any other protocol deviation that results in a significant risk to the patient's safety
- Study Terminated by Sponsor
- Patient/guardian decision
- Physician decision
- Lost to follow-up
- Death

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

- Progression of disease (radiological assessment by investigator)
- Technical Problems
- Protocol deviation

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Table 7-1. If they fail to return for unknown reasons, every effort (e.g., telephone, email, letter) should be made to contact them as specified in Section 7.1.5.4.

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

Patients who discontinue study treatment during the treatment phase should be scheduled for a visit as soon as possible and within 7 days after the last dose of study treatment, at which time all of the assessments listed for the EOT visit will be performed. If a patient withdraws from treatment at a study visit, EOT assessments do not need to be repeated. An End of Treatment Phase Disposition eCRF page should be completed, giving the date and reason for stopping LDK378 treatment.

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

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

Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

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

Patients who discontinue study treatment should enter the survival follow-up period or continue tumor assessments when appropriate. Tumor assessments will continue until

[redacted]

progression of disease (radiological as assessed by investigator), patient withdraws consent from tumor assessments, patient is lost to follow-up, death or study terminated by Sponsor.

7.1.3.1 Replacement policy

Patients lost to follow-up or withdrawing consent from the study without observed events for efficacy endpoints (e.g. PFS) will be censored for the data analysis and will not be replaced.

7.1.4 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

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

7.1.5 Follow up period

7.1.5.1 Safety follow up

All patients will be followed for AEs and SAEs for at least 30 days following the last dose of study treatment at the end of treatment phase.

At the end of this period, the investigator should assess and discuss with the patient any AE observed/concomitant medication taken since discontinuation of study treatment.

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

7.1.5.2 Post-treatment follow-up

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

[redacted]

7.1.5.3 Survival follow-up

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

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

7.1.5.4 Lost to follow-up

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

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.1 (Appendix 2) based on RECIST 1.1 (Eisenhauer et al 2009).

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

7.2.1.1 Baseline imaging (+/- photography) assessment

Imaging assessments will be performed at screening/baseline Day -28 to Day -1 prior to Cycle 1 Day 1.

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

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

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

[redacted]

- Photography (for any skin lesions) if clinically significant

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

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

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

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

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

7.2.1.2 Subsequent imaging for response assessment

Tumor evaluations as described in Table 7-2 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1).

Tumor assessment for response determination will be made every 8 weeks starting from Day 1 of Cycle 3 (+/- 7 days window). **The 8 weeks interval should be respected regardless of whether treatment with LDK378 is temporarily withheld.**

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

Each lesion that is measured at baseline must be measured by the same method (either same radiological method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document PD per RECIST 1.1 (Appendix 2).

Table 7-2 Imaging assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI (Chest, Abdomen)	Mandated	every 8 weeks
Whole bone scan	Mandated	If clinically indicated
Brain CT or MRI	Mandated	Cycle 3 then every 2 cycle (i.e. every 8 weeks): only if positive at baseline or clinically indicated only if positive at baseline or clinically indicated.
• CT scan or MRI of other metastatic sites (e.g. neck, pelvis, etc) • Localized bone CT scan, MRI or x-ray (for any lesions identified on the whole body bone scan that are not visible on the chest/abdomen CT scan or MRI)	if clinically indicated	Cycle 3 then every 2 cycle (i.e. every 8 weeks): only if positive at baseline or clinically indicated only if positive at baseline or clinically indicated.

7.2.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. For details on AE collection and reporting, refer to Section 8. Significant findings that were present prior to the signing of informed consent must be included in the relevant medical history/current medical conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF. All safety assessments at Cycle 1 Day1 have to be conducted prior to start of the first dose of LDK378, unless otherwise specified.

7.2.2.1 Physical examination

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

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

7.2.2.2 Vital signs

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

For the assessment schedule refer to Table 7-1.

[redacted]

7.2.2.3 Height and weight

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

7.2.2.4 Performance status

WHO performance status will be assessed as per the assessment schedule (refer to Table 7-1). Assessment of WHO performance status (Table 7-3) will be performed within the time windows described above of the scheduled assessment, even if study treatment is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 7-3 WHO performance status scale

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

7.2.2.5 Laboratory evaluations

Local laboratories will be used for the analysis of scheduled hematology, biochemistry and other blood specimens collected as part of safety monitoring (as detailed in Table 7-1). Dipstick urinalysis will also be performed locally. Laboratory values obtained during the Screening phase will be used to assess patient's eligibility. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 7.1).

[redacted]

Table 7-4 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Red blood cells, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils in percentage or absolute)
Chemistry	Albumin, ALT (SGPT), AST (SGOT), calcium, creatinine, creatinine clearance, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, fasting glucose, phosphate(inorganic phosphorus), alkaline phosphatase, amylase, lipase, GGT
Urinalysis	Macroscopic Panel (Dipstick) (Color, bilirubin, Blood, Glucose, Ketones, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)
Coagulation	Pro-thrombin time (PT) and International normalized ratio (INR) or Quick Test
Pregnancy	At screening visit, serum pregnancy test At subsequent cycles, urinary pregnancy test.
Hormones (males only)	Testosterone (total and free), LH, Follicle-stimulating hormone (FSH)

7.2.2.5.1 Hematology

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

7.2.2.5.2 Clinical chemistry

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

7.2.2.5.3 Urinalysis

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

7.2.2.5.4 Pregnancy and assessments of fertility

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

Women who are determined not to be of child bearing potential before the study will only be tested at screening. When non-child bearing potential status is determined during the study, further pregnancy testing will not be continued. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential (such testing is not covered

[redacted]

as part of the study assessments). If local requirements dictate otherwise, local regulations should be followed.

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

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

7.2.2.5.5 Hormones

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

7.2.2.5.6 Coagulation

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

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

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

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

The triplicate ECGs should be taken approximately 2-4 minutes apart.

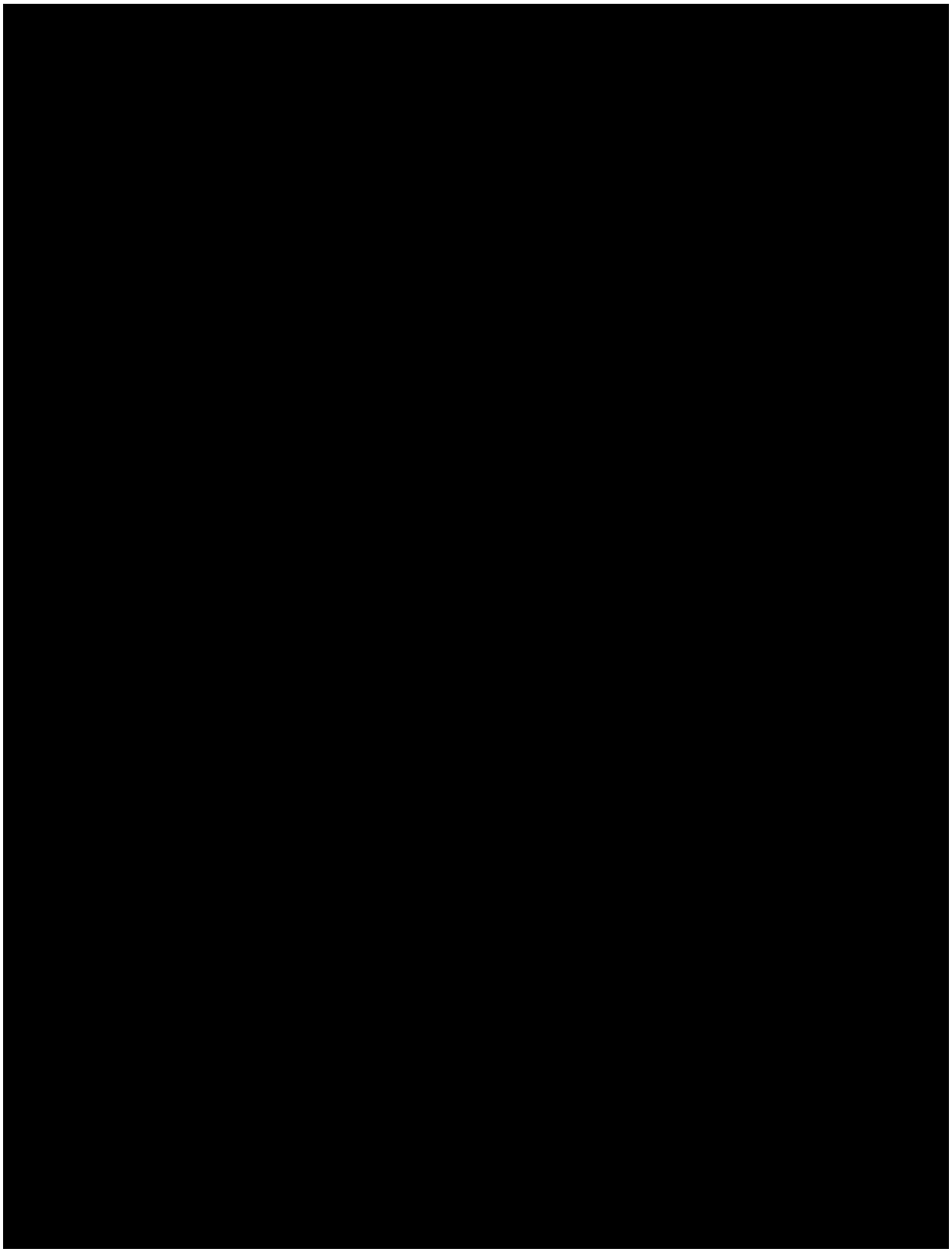
Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. An ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site.

Table 7-5 Local ECG collection plan

Cycle	Day	Time	ECG Type
Screening	-28 to -1	Anytime	12 Lead
1	1	Pre-dose	12 Lead
1	15	Pre-dose	12 Lead
2	1	Pre-dose	12 Lead
3	1	Pre-dose	12 Lead
Subsequent cycles and EOT	1	Pre-dose	12 Lead

Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

[redacted]



[redacted]

[redacted]

7.2.5 Resource utilization

Not applicable

[redacted]

7.2.6 Patient reported outcomes

Not applicable

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

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

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse event.

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

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

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

1. The severity grade (CTCAE Grade 1-4)

[redacted]

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

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

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

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

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

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

[redacted]

8.1.3 Adverse events of special interest

The adverse events of special interest to be monitored for LDK378 have also been identified and include: hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia, pancreatitis (including lipase and amylase elevations); and GI toxicity (nausea, vomiting and diarrhea). Details regarding these adverse events are provided in the Investigator's Brochure for LDK378. Potential emergent new AEs will be monitored during the course of the study.

8.2 Serious adverse events

8.2.1 Definitions

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

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

8.2.2 Reporting

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

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

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically

[redacted]

thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and send submit the completed, form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

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

8.3 Emergency unblinding of treatment assignment

Not applicable. This is an open-label study.

8.4 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment 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.

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

[redacted]

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

8.5 Warnings and precautions

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

8.6 Data Monitoring Committee

Not applicable

8.7 Steering Committee (SC)

A SC, comprised of Investigators in NSCLC management from the study will be formed. The purpose of the SC is to provide overall guidance regarding design of the study, conduct and execution of the trial to include (but not limited to) safety, accrual and contribution to scientific input for publications. Responsibilities of the SC and communication flow between the SC and Novartis will be included in the SC charter document.

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

[redacted]

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

9.2 Site monitoring

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

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

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

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (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.

[redacted]

9.4 Database management and quality control

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

[redacted]

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

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

10 Statistical methods and data analysis

The data from all participating centers in this protocol will be combined. The primary analysis of study data will be conducted at the time when all patients have either completed at least 6 cycles of treatment or discontinued earlier. All available data from all patients up to this cutoff date will be analyzed. The final analysis of study data will be conducted at the end of the study (Section 4.3). These data will be summarized in the CSR.

[redacted]

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) will include all patients who receive at least one dose of LDK378. The FAS will be used for summaries of baseline characteristics and all efficacy analyses, unless otherwise specified.

10.1.2 Safety Set

The Safety Set will include all patients who receive at least one dose of LDK378. All safety data will be analyzed using the safety set. In this non-randomized study the FAS and safety set are identical.

10.1.3 Per-Protocol Set

Not applicable

10.1.4 Dose-determining analysis set

Not applicable

[redacted]

10.2 Patient demographics/other baseline characteristics

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

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for the analyses below.

The actual dose and duration of LDK378, as well as the dose intensity (computed as the ratio of total dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity), will be listed and summarized. Dose reductions and dose delays (including the reasons for these) will be listed and summarized.

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

10.4 Primary objective

The primary objective is to demonstrate the antitumor activity of LDK378 in patients with ALK-positive non-small cell lung cancer (NSCLC) previously treated with alectinib.

[redacted]

10.4.1 Variable

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

10.4.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be performed on the FAS. The primary efficacy endpoint ORR will be estimated and reported along with the exact (Clopper-Pearson) 95% confidence interval (CI). No statistical hypothesis testing is planned.

10.4.3 Handling of missing values/censoring/discontinuations

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

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

Patients who have disease progression and continue to receive the study treatment after progression will qualify for progressive disease at the time of first documented progression. Tumor assessments performed after the first documented progression will not be considered for ORR. This will apply to secondary efficacy endpoints as well.

10.4.4 Supportive analyses

The best overall response will be listed by patient and summarized along with the ORR.

10.5 Secondary objectives

All secondary efficacy analyses will be performed on the FAS, unless otherwise specified.

10.5.1 Key secondary objective(s)

Disease control rate

Disease control rate (DCR) is defined as the proportion of patients with a best overall response of CR, PR or SD, as assessed per RECIST 1.1 by the investigator. DCR will be estimated and reported along with the exact 95% CI.

Duration of response

Among patients with a confirmed response (PR or CR) per RECIST 1.1 by the investigator, the duration of response (DOR) is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause. DOR will be listed by patient and will be described using Kaplan-Meier methods and relevant summary statistics such as median DOR and the 95% CI. Censoring rules for DOR follow those for PFS.

[redacted]

Time to response

Among patients with a confirmed response (PR or CR) per RECIST 1.1 by the investigator, the time to response (TTR) is defined as the time from the date of the first dose of LDK378 to first documented response (PR or CR). TTR will be listed by patient and will be summarized using descriptive statistics for patients with a confirmed response.

10.5.2 Other secondary efficacy objectives

Progression-free survival

Progression-free survival (PFS) is defined as the time from the date of first dose of LDK378 to the date of first documented disease progression per RECIST 1.1 or death due to any cause. A patient who has not progressed or died at the date of the analysis or when he/she receives any further anticancer therapy in the absence of disease progression will be censored at the time of the last adequate tumor evaluation before the earlier of the cut-off date or the anticancer therapy date. By default, if disease progression or death for any reason is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression or death for any reason is documented after two or more missing tumor evaluations, the PFS time of these patients will be censored at the date of the last adequate tumor evaluation without PD. Censoring rules will be detailed in the RAP. PFS will be listed by patient and will be described using Kaplan-Meier methods and relevant summary statistics such as median PFS and the 95% CI.

Overall survival

Overall survival (OS) is defined as the time from the date of first dose of LDK378 to the date of death due to any cause. OS time for patients who are alive at the end of the study or are lost to follow-up will be censored at the date of last contact. OS will be listed by patient and will be described using Kaplan-Meier methods and relevant summary statistics such as median OS and the 95% CI.

Overall intracranial response rate

Overall intracranial response rate (OIRR) is calculated based on response assessments in the brain for patients having measurable brain metastases at baseline (i.e. at least one target lesion in the brain). OIRR is defined as the ORR based on target, non-target and new lesions in the brain and defined as the proportion of patients with a best overall confirmed response of CR or PR in the brain, as assessed per RECIST 1.1 by the investigator. OIRR will be estimated and reported along with the exact 95% CI. The best overall intracranial response will be listed by patient and will be summarized along with the OIRR. These analyses will be conducted for patients with measurable brain metastases at baseline.

[redacted]

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

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

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

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

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

10.5.3.2 Adverse events (AEs)

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

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

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment. For each specified category, the number and percentage of patients with at least one event per category will be summarized.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. In the unlikely case when a local laboratory normal range overlaps into the higher (i.e. non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero. Grade 5 will not be used.

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

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

- shift tables using CTCAE grades to compare baseline to the worst on-treatment value

[redacted]

- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges will be generated.

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

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

10.5.3.4 Other safety data

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

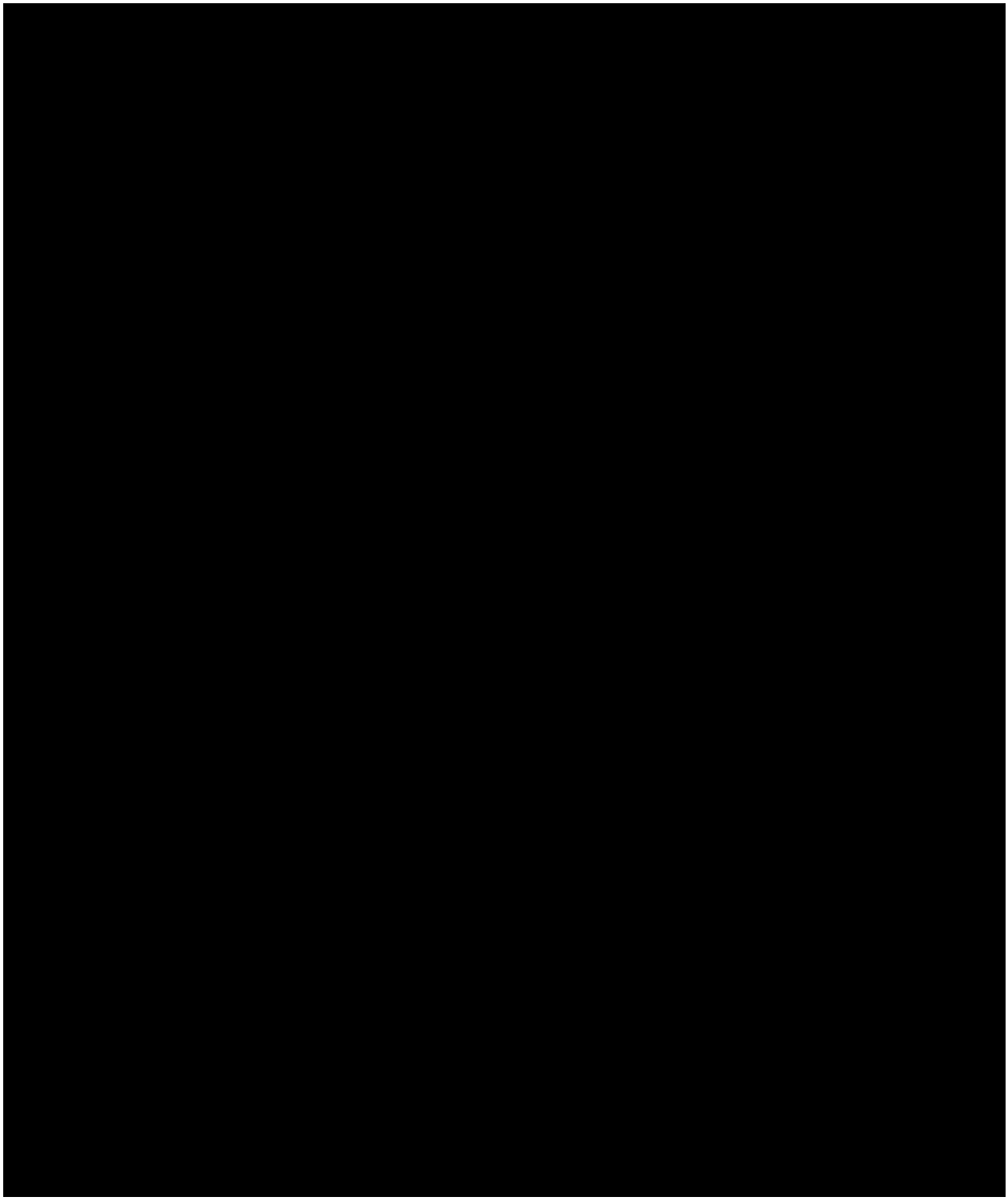
10.5.3.5 Tolerability

Tolerability will be evaluated in terms of dose reductions or drug interruptions due to an AE.

[redacted]

[redacted]

[redacted]



10.7 Interim analysis

No interim analysis is planned in this study.

10.8 Sample size calculation

The study does not include formal statistical hypothesis testing and the sample size (N=20) is not derived based on power considerations.

A response rate of 10% or less is considered as an insufficient level of activity for the proposed patient population. With a sample size of 20 patients, there is an approximately 58.4% chance that the exact 95% CI will exclude an insufficient response rate of 10% when the true ORR is 30%. The probability increases to 75.5% and 87.4%, when the true ORRs are 35% and 40%, respectively. For an observed response rate of 30.0% (6 responders in 20 patients), the exact 95% CI is (11.9%, 54.3%). The operating characteristics of this study are summarized in Table 10-1.

Table 10-1 Operating characteristics for various ORRs when N=20 patients

True ORR	Probability that exact 95% CI excludes an insufficient level of 10%*	Expected number of responders	Observed ORR and exact 95% CI
30%	58.4%	6	30.0% (11.9%, 54.3%)
35%	75.5%	7	35.0% (15.4%, 59.2%)
40%	87.4%	8	40.0% (19.1%, 63.9%)

*Of 20 patients at least 6 responders are required to meet the criteria (i.e., exact 95% CI excludes an insufficient level of 10%), thus it is calculated as a binomial probability that ≥6/20 responders are observed given the true ORR.

10.9 Power for analysis of key secondary variables

Not applicable

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is 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 CRFs.

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

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

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis 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 case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports.

Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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

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

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

[redacted]

12 Protocol adherence

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

12.1 Amendments to the protocol

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

[redacted]

13 References (available upon request)

[Beson Al, Ajani JA, Catalano RB, et al. (2004)] Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea, J Clin Oncol 22:2918-26

[Brambilla, et al. (2014)] World Cancer Report, Stewart BW, Wild CP (Eds), World Health Organization, Lyon 2014

[Brookmeyer R, Crowley J (1982)] A Confidence Interval for the Median Survival Time, Biometrics 38: 29-41

[Eisenhauer, et al. (2009)] New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer; 45; 228–47

[EMA Guideline on the Investigation of Drug Interactions (2012)]

[Ettinger DS, Akerley W, Bepler G, et al. (2010)] NCCN Non-Small Cell Lung Cancer Panel Members. J Natl Compr Canc Netw. 2010 Jul;8(7):740-801. Review. No abstract available

[FDA draft guidance (2012)] Drug interaction studies: study design, data analysis, implications for dosing, and labeling recommendations.

[Felip E, Kim DW, Mehra R, et al. (2014)] Efficacy and Safety of Ceritinib in Patients with Advanced Anaplastic Lymphoma Kinase (ALK)-rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC): An Update of ASCEND-1 (Internet) Available from: < oncologypro.esmo.org/Meeting-Resources/ESMO-2014/NSCLC-Metastatic/Evaluation-of-ceritinib-treated-patients-pts-with-anaplastic-lymphoma-kinase-rearranged-ALK-non-small-cell-lung-cancer-NSCLC-and-brain-metastases-in-the-ASCEND-1-study> (Accessed 08 Dec 2014)

[Gettinger S, Lynch T (2011)] A decade of advances in treatment for advanced non-small cell lung cancer. Clin Chest Med; 32(4):839-51

[Howlader N, Noone AM, Krapcho M, et al. (eds) (2009)] National Cancer Institute SEER cancer statistics review 1975-2009 (Vintage 2009 populations) (Internet) Available from: < seer.cancer.gov/csr/1975_2009_pops09/> (Accessed 22 February 2013)

[Katayama R, Friboulet L, Koike S, et al. (2014)] Two Novel ALK Mutations Mediate Acquired Resistance to the Next-Generation ALK Inhibitor Alectinib. Clin Cancer Res; 20(22): 1–11

[Malvezzi M, Bertuccio P, Levi F, et al. (2012)] European cancer mortality predictions for the year 2012. Ann Oncol; 23(4):1044-52

[Ministry of Health, Labour and Welfare Population Survey Report (2013)] (Internet) Available from: < http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai13/dl/h6.pdf > (last accessed on 26-Sep-2014)

[Mok T, Kim DW, Wu YL, et al. (2014)] First-line crizotinib versus pemetrexed–cisplatin or pemetrexed–carboplatin in patients (pts) with advanced *ALK*positive non-squamous non-small cell lung cancer (NSCLC): results of a phase III study (PROFILE 1014). J Clin Oncol 32:5s, 2014 (suppl; abstr 8002)

[Murakami H, Seto T, Takahashi T, et al. (2014)] Phase I Study for Ceritinib (LDK378) in Japanese Patients with ALK Genetic Alterations (Internet) Available from: <

[redacted]

oncologypro.esmo.org/Meeting-Resources/ESMO-2014/NSCLC-Metastatic/Phase-I-study-for-ceritinib-LDK378-in-Japanese-patients-with-ALK-genetic-alterations> (Accessed 08 Dec 2014)

[National Comprehensive Cancer Network] NCCN Clinical Practice Guidelines in Oncology Non-Small Cell Lung Cancer (Version 3. 2012) (Internet) Available from nccn.org Accessed 07/29/2012.

[Nguyen KS, Sanford RA, Huberman MS, et al. (2012)] Patterns of care for non-small-cell lung cancer at an academic institution affiliated with a national cancer institute-designated cancer center. J Oncol Prac; 8(1):57-62

[Ou SH (2011)] Crizotinib a novel and first-in-class multitargeted tyrosine kinase inhibitor for the treatment of anaplastic lymphoma kinase rearranged non-small cell lung cancer and beyond. Drug Des Devel Ther; 5:471-85

[Scagliotti G, Stahel RA, Rosell R, et al. (2012)] ALK translocation and crizotinib in non-small cell lung cancer: An evolving paradigm in oncology drug development. Eur J Cancer; 48(7):961-73

[Seto T, Kiura K, Nishio M, et al. (2013)] CH5424802 (RO5424802) for patients with *ALK*-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1–2 study. Lancet Oncol 2013;14:590–8

[Shaw AT, Mehra R, Kim D-W, et al. (2013)] Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC [abstract]. J Clin Oncol 31 (suppl); 8010A

[Shaw AT, Yeap BY, Mino-Kenudson M, et al. (2009)] Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4- ALK. J Clin Oncol; 27:4247-53

[Siegel R, Naishadham D, Jemal A (2012)] Cancer statistics, 2012. CA Cancer J Clin; 62(1):10-29

[Soda M, Choi YL, Enomoto M (2007)] Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature; 448(7153):561-6

[Takeuchi K, Choi YL, Togashi Y, et al. (2009)] KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res; 15(9):3143-9

[Zhang X, Zhang S, Wu YL, et al. (2010)] Fusion of EML4 and ALK is associated with development of lung adenocarcinomas lacking EGFR and KRAS mutations and is correlated with ALK expression. Mol Cancer. 2010 Jul 13;9:188. doi: 10.1186/1476-4598-9-188

14 Appendices:

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

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

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

* Compounds known to increase QTc interval that are also primarily metabolized by CYP3A4/5. For an updated list of CYP2C9 substrates, CYP3A substrates, inhibitors and inducers, please reference the Novartis Oncology Clinical Pharmacology internal memo: drug-drug interactions (DDI) database, Oct 2010, which is compiled primarily from the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database.

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

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

[redacted]

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

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

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

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

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

[redacted]

Table 14-4 List of prohibited QT prolonging drugs

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

Please note: *CYP3A substrate Source: Arizona Center for Education and Research on Therapeutics (CERT), Drugs that prolong the QT interval and/or induce Torsades de Pointes, http://.azcert.org/medical-pros/drug-lists/drug-lists.cfm

[redacted]

15 Appendices

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

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

Document type: TA Specific Guideline

Document status: Version 3.1: 29-Nov-2011
Version 3:0: 19-Oct-2009
Version 2:0: 18-Jan-2007
Version 1:0: 13-Dec-2002

Release date: 29-Nov-2011

Authors (Version 3.1): [redacted]

Authors (Version 3): [redacted]

Authors (Version 2): [redacted]

Authors (Version 1): [redacted]

[redacted]

Glossary

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

[redacted]

15.1.1 Introduction

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

The efficacy assessments described in Section 15.1.2 and the definition of best response in Section 15.1.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 15.1.18 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 15.1.28 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

15.1.2 Efficacy assessments

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

15.1.3 Definitions

15.1.4 Disease measurability

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

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

For patients without measurable disease see Section 15.1.26.

Measurable lesions (both nodal and non-nodal)

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

[redacted]

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

15.1.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 15.1.26.

15.1.6 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

[redacted]

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions

[redacted]

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

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

15.1.7 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 15.1.4.
- **Nodal target**: See Section 15.1.4.

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

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

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

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

[redacted]

for the target (Table 15-1) and non-target lesions (Table 15-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 15-3) as well as the presence or absence of new lesions.

15.1.9 Follow-up and recording of lesions

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

15.1.10 Non-nodal lesions

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

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

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

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

15.1.11 Nodal lesions

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

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

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

[redacted]

15.1.12 Determination of target lesion response

Table 15-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.[1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.[2]
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1.] SOD for CR may not be zero when nodal lesions are part of target lesions

[2.] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR

[3.] Methodology change See Section 15.1.6.

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 15-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the

[redacted]

remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

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

15.1.13 Determination of non-target lesion response

Table 15-2 Response criteria for non-target lesions

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

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

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 15.1.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

15.1.14 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm

[redacted]

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 (see Section 15.1.15).
- A lymph node is considered as a "new lesion" and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 15.1.6.

15.1.15 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 15-3.

Table 15-3 Overall lesion response at each assessment

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

[1.] This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2.] Once confirmed PR was achieved, all these assessments are considered PR.
[3.] As defined in Section 15.1.8.

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

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

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

[redacted]

15.1.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 15.1.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

15.1.17 Best overall response

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

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

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

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).

[redacted]

- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

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

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

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

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

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

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

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

[redacted]

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

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

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

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

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

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

15.1.18 Time to event variables

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

15.1.19 Progression-free survival

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

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

15.1.20 Overall survival

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

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

15.1.21 Time to progression

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

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

15.1.22 Time to treatment failure

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

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

15.1.23 Duration of response

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

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such

as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

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

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

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

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

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

15.1.24 Time to response

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

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 15.1.23. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

[redacted]

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

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

Assessment date

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

Start dates

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

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

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 15.1.26).

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

Date of discontinuation is the date of the end of treatment visit.

[redacted]

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

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

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 15-4.

Table 15-4 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 15.1.8.

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

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

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

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses

[redacted]

which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

15.1.27 Sensitivity analyses

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

Based on definitions outlined in Section 15.1.25, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics-April 2005) as a reference, the following analyses can be considered:

[redacted]

Table 15-5 Options for event dates used in PFS, TTP, duration of response

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

[1]=Definitions can be found in Section 15.1.25.
[2]=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 15.1.25.
[3]=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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

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

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

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

[redacted]

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

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

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 15-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

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

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

15.1.28 Data handling and programming rules

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

15.1.29 Study/project specific decisions

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

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

15.1.30 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source

[redacted]

documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

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

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

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

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

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

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

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

15.1.32 Medical validation of programmed overall lesion response

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

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

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

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

15.1.33 Programming rules

The following should be used for programming of efficacy results:

15.1.34 Calculation of 'time to event' variables

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

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

15.1.35 Incomplete assessment dates

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

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 15.1.25). If all measurement dates have no day recorded, the 1st of the month is used.

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

15.1.36 Incomplete dates for last known date patient alive or death

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

[redacted]

15.1.37 Non-target lesion response

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

15.1.38 Study/project specific programming

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

15.1.39 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 15-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 15.1.25. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

[redacted]

15.1.40 References (available upon request)

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

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

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

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

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

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

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

[redacted]