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Novartis Research and Development

INC280/Capmatinib

Clinical Trial Protocol CINC280A2204 / NCT04677595

A phase II, multicenter, two-cohort study of oral *MET* inhibitor capmatinib in Chinese adult patients with *EGFR* wild-type (wt), *ALK* rearrangement negative, *MET* exon 14 skipping mutations, advanced non-small cell lung cancer (NSCLC) who are treatment naive or failed one or two prior lines of systemic therapy

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List of abbreviations

ADL	Activities of Daily Living
AE(s)	Adverse Event(s)
AESI	Adverse Event of Special Interest
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANC	Absolute Neutrophil Count
Anti-HBc	Anti-Hepatitis B core antibody
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine Triphosphate
AUC	Area Under Curve
AUC_{inf}	Area under the plasma (serum, or blood) concentration versus time curve from time zero to infinity
BAL	Bronchoalveolar Lavage
BCG	Bacillus Calmette-Guerin
BCRP	Breast Cancer Resistance Protein
b.i.d	Bis In Die/twice daily
BIRC	Blinded Independent Review Committee
BOIR	Best Overall Intracranial Response
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
CAP	Chest Abdomen Pelvis
CDx	Companion Diagnostic
CFR	Code of Federal Regulation
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum (peak) concentration of drug in plasma
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
CO	Country Organization
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease of 2019.
CR	Complete Response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRS	Case Retrieval Strategy
CSCO	Chinese Society of Clinical Oncology
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events

ctDNA	Circulating Tumor DNA
CTT	Clinical Trial Team
CV	Coefficient of Variation
CYP1A2	Cytochrome P450 1A2
CYP3A	Cytochrome P450 3A
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DDI	Drug-Drug Interactions
DILI	Drug-Induced Liver Injury
DLCO	Diffusing capacity of the Lungs for Carbon monoxide
DLTs	Dose-Limiting Toxicities
DNA	Deoxyribonucleic Acid
DOIR	Duration Of Intracranial Response
DOR	Duration Of Response
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
EQ VAS	EuroQoL visual analogue scale
EQ-5D-5L	EuroQoL-5 Dimension-5 Level
ERCP	Endoscopic Retrograde Cholangio-Pancreatography
eSource	Electronic Source
EU	European Union
FAS	Full Analysis Set
FAS-BM	Full Analysis Set - Brain Metastases
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin Fixed Paraffin Embedded
FPFV	First Patient First Visit
FUP	Follow-Up
GCN	Gene Copy Number
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GGT	Gamma-Glutamyl Transferase
GI	Gastro-Intestinal
GLDH	Glutamate Dehydrogenase
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HA	Health Authorities
HAV	Hepatitis A
HBsAg	Hepatitis B virus surface Antigen

HBV	Hepatitis B
HCV	Hepatitis C
HEV	Hepatitis E
Hgb	Hemoglobin
HGF	Hepatic Growth Factor
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSV	Herpes Simplex Virus
i.v.	Intravenous
IB	Investigator's Brochure
IC	Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	Identity
IDCR	Intracranial Disease Control Rate
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
KM	Kaplan-Meier
LC/MS/MS	Liquid Chromatography coupled to tandem Mass Spectrometry
LC13	Lung Cancer 13 (specific module of EORTC QLQ)
LFT	Liver Function Test
LLCI	Lower Limit of Confidence Interval
LLN	Lower Limit of Normal
LLOQ	Lower Limit Of Quantification
LPLV	Last Patient Last Visit
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal Epithelial Transition
*MET*Δex14	*MET* exon 14-skipping
MRI	Magnetic Resonance Imaging
NCCN FACT-FBrSI	National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy - Brain Symptom Index
NCI	National Cancer Institute

NDA	New Drug Application
NSCLC	Non-Small Cell Lung Cancer
NTI	Narrow Therapeutic Index
OIRR	Overall Intracranial Response Rate
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PBPK	Physiology-Based Pharmacokinetics
pCO2	Partial pressure of carbon dioxide in blood
PD	Progressive Disease
PD-1	Programmed cell Death protein 1
PD-L1	Programmed Death-Ligand 1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PFT	Pulmonary Function Tests
P-gp	Permeability-GlycoProtein
PK	Pharmacokinetic(s)
PLT	Platelets
pO2	Partial pressure of oxygen in blood
PR	Partial Response
PRO	Patient Reported Outcomes
PS	Performance Status
PT	Prothrombin Time
QLQ	Quality of Life Questionnaire
QMS	Quality Management System
QoL	Quality of Life
QT	Quick Test
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RANKL	Receptor Activator of Nuclear factor Kappa-B Ligand
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RAP	Report and Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
ROS1	Proto-oncogene tyrosine-protein kinase ROS (Reactive Oxygen Species)
RP2D	Recommended Phase II Dose
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
SD	Stable Disease
Site No.	Site Number
SMQ	Standardized MedDRA (Medical dictionary for regulatory activities) Query
SOP	Standard Operating Procedures

SUSAR	Suspected Unexpected Serious Adverse Reaction
TdP	Torsades de Pointes
TKI	Tyrosine Kinase Inhibitor
T_{max}	Maximum drug concentration
TSH	Thyroid Stimulating Hormone
TTE	Time To Event
TTIR	Time to Intracranial Response
TTR	Time To Response
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization
WHS	White coat Syndrome / White coat Hypertension
wt	Wild-type

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy).
Assessment	A procedure used to generate data required by the study.
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time.
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q21 days).
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 400 mg twice daily).
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which main informed consent must be obtained. The action of enrolling one or more participants.
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Investigational drug/ treatment	The drug whose properties are being tested in the study.
Medication number	A unique identifier on the label of medication kits.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy).
Participant	A trial participant (a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection.
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.

Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Remote	Describes any trial activities performed at a location that is not the investigative site.
Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Stage of 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.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant’s privacy rights are described in the corresponding informed consent form.

Amendment 03 (07-Jul-2022)

Amendment rationale

As of the release date of this amendment, 22 participants have been enrolled, 15 in the cohort I and 7 in the cohort II. Of these 13 are on treatment and 9 discontinued study treatment.

The main purpose of this amendment is to clarify that the centralized *MET*Δex14 data from tumor tissue analysis may be utilized towards development of an *in vitro* diagnostic test for *MET*Δex14, such as a companion diagnostic. In addition to the blood collected at C1D1, remnant tissue material or extracted nucleic acid material from tumor tissue samples collected for centralized *MET*Δex14 testing may also be used towards companion diagnostic development purposes (dependent on health authority approval).

Furthermore, an additional eligibility criterion was added to exclude participants who received live vaccines within 30 days prior to the first dose of study treatment, and to add live vaccines as prohibited concomitant therapy while a participant is dosed with the study treatment and for 30 days after the last dose of study treatment. Patients with advanced NSCLC with METΔex14 mutation are typically an elderly and vulnerable patient population (Awad et al 2019). Based on the vaccine risk assessment undertaken for this patient population, these patients may be less immunocompetent due to the multiple confounding factors such as advanced age, advanced stage of NSCLC and prior exposure to antineoplastic therapy. Hence, live vaccines are not recommended in this patient population. The exclusion criteria and guidance on use of live vaccines as concomitant medications have been updated accordingly.

Also, in exclusion criteria, additional instructions have been added and some rewording done for improved clarity (including clarification based on health authority feedback).

Finally, the SAE reporting criteria have been detailed in accordance with current regulatory requirements based on health authority feedback. Initial and follow-up SAE must be notified to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of learning of its occurrence. (Note: if more stringent, local regulations regarding reporting timelines prevail).

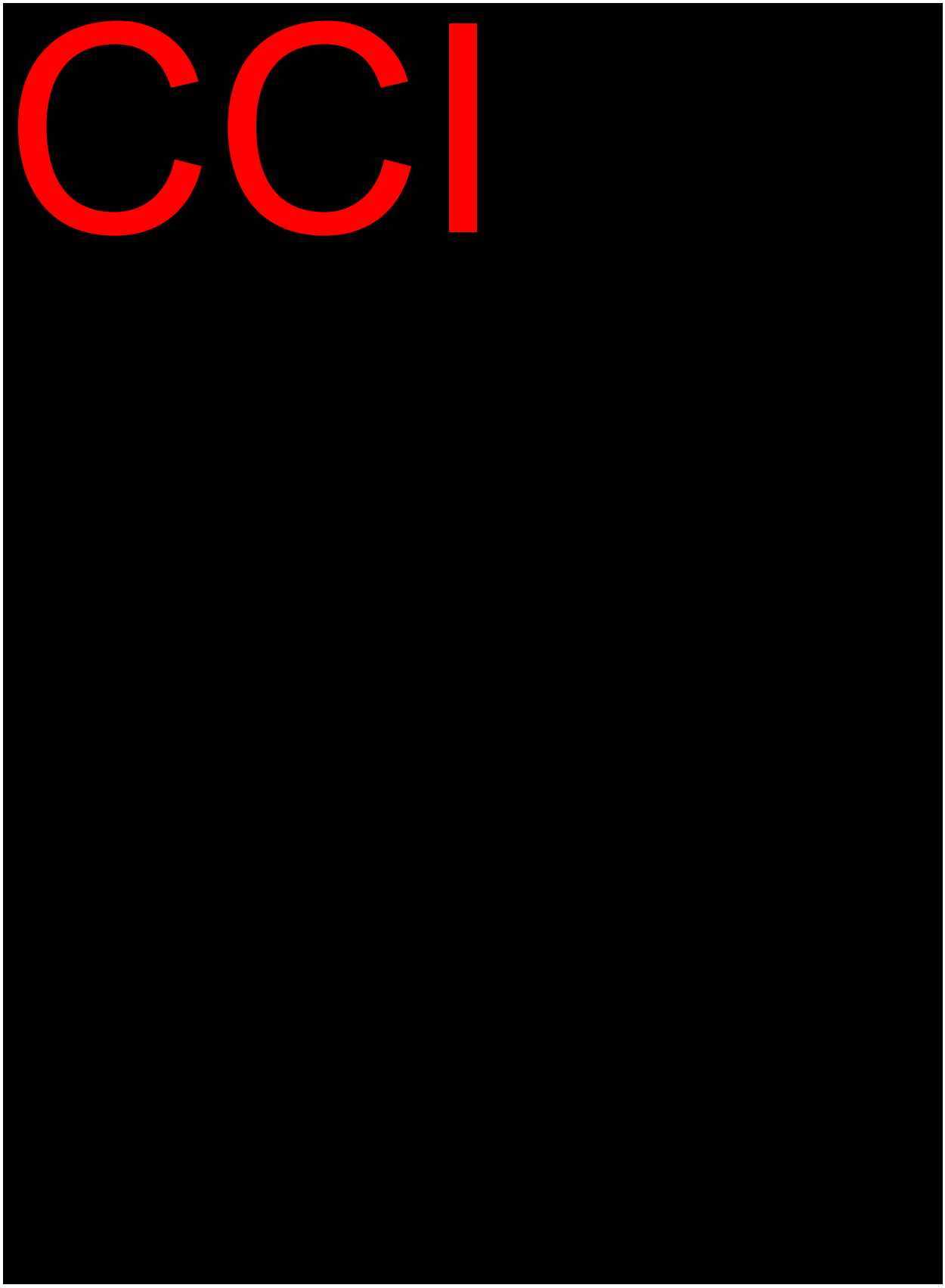
Other editorial revisions and text corrections were made throughout the protocol for clarification, where required.

Changes to the protocol

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

The following changes have been implemented and the protocol has been updated to reflect all significant changes below based on the current Novartis protocol template version 5.0 used as reference:

CCI


CCI


CCI


CCI

IRBs/IECs

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

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

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

Amendment 02 (18-May-2021)

Amendment rationale

As of the release date of this amendment, 1 participant has been pre-screened and no participants have been treated in this study.

This amendment is triggered by the release of the results of the analytical validation of a specific 11-1 PCR assay used to test for *MET*Δex14 mutation status.

This amendment includes the following revisions:

- Adequate number of fresh-cut tumor tissue slides required to be submitted to the Novartis designated laboratory to test for *MET*Δex14 mutation status. All tissue samples need to have >20% tumor content per slide.
  - If resection sample, 5 slides requested initially and if sufficient tumor material is not found to perform the *MET*Δex14 mutation analysis, additional slides (not exceeding a total of 10 slides overall) will be requested.
  - If core needle biopsy, 10 slides requested per participant. This change is based on the 11-1 PCR assay validation results that showed the need of 5 to10 slides with minimum of 20% of tumor content for generating adequate RNA input for the assay. Tissue samples with low tumor content (i.e. less than 20% tumor content) may not be evaluable for *MET*Δex14 mutation analysis.
- Only slides can be submitted, not blocks
- Removal of mandatory band testing as part of hematology assessment
- New section added for public health emergencies as rationale for Public Health Emergency mitigation procedures
- Estimand language added due to recent decision to include estimand framework in every protocol moving forward aimed for Chana's State Food and Drug Administration (CFDA China)
- Alignment with most recent one CTP version 4 protocol template where required

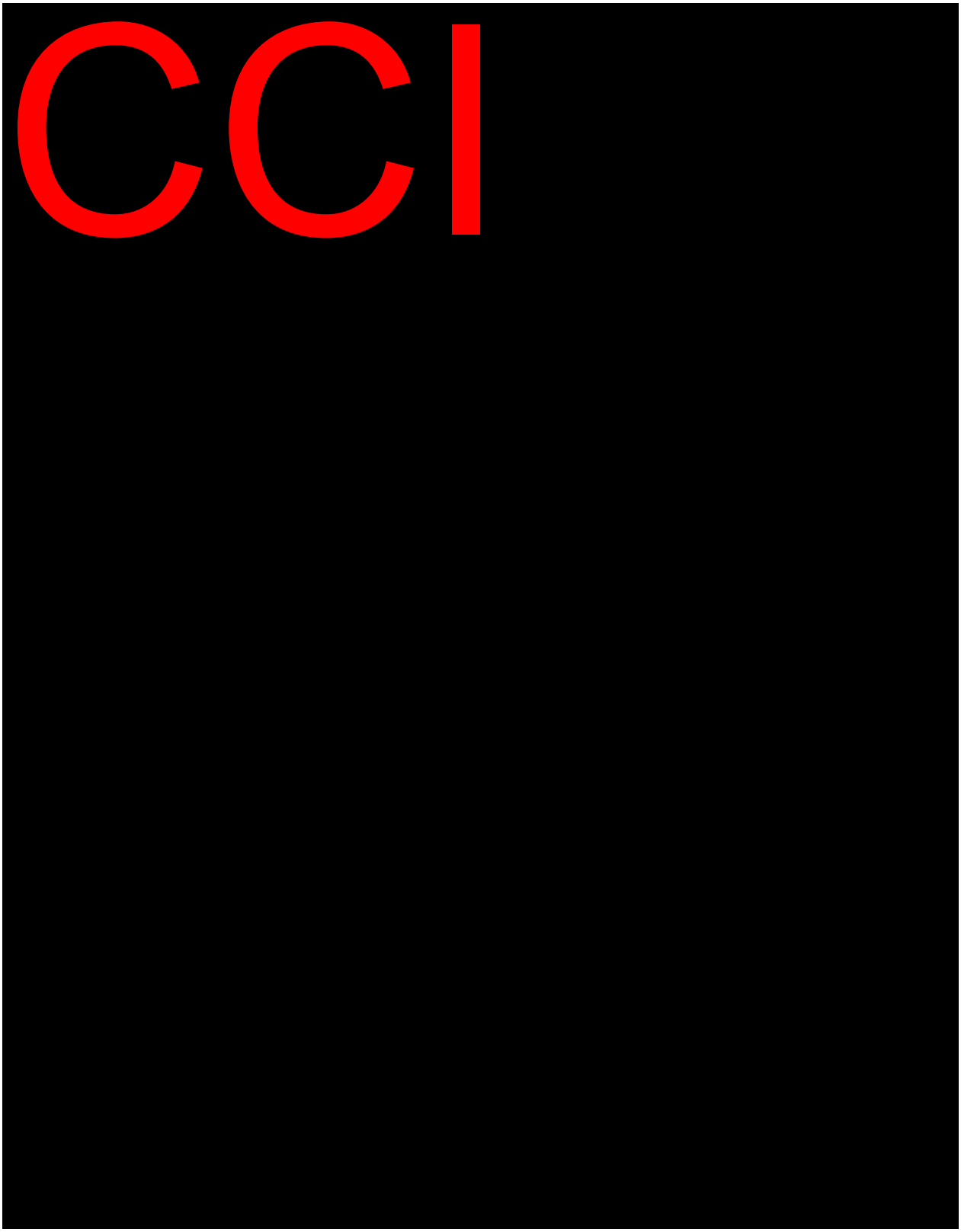
Changes to the protocol

The assessment of the benefit-risk concluded the absence of additional risks related to COVID-19.

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

The following sections of the protocol were changed:


CCI


CCI

IRBs/IECs

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

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

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

Amendment 01 (19-Jun-2020)

Amendment rationale

As of the release date of this amendment, no participants have been screened or treated in this study.

This amendment addresses the following revisions:

- Decreased the number of tumor tissue slides required to be submitted to the Novartis designated laboratory to test for *MET*Δex14 mutation status from at least 10 slides to 5 slides per participant
- Novartis guidelines released on Response Assessment in Neuro-oncology (RANO) for Brain Metastases (BM). Guidelines have been added as an appendix to the protocol to support the secondary endpoint assessing intracranial anti-tumor activity of capmatinib in participants with Central Nervous System (CNS) lesions
- Update of the definitions of duration of response (DOR), time to intracranial response (TTIR) and duration of intracranial response (DOIR) to align with the RANO-BM guidelines (Appendix 2)

Changes to the protocol

The following sections of the protocol were changed:

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

IRBs/IECs

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

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

Protocol summary

Protocol number	CINC280A2204
Full Title	A phase II, multicenter, two-cohort study of oral *MET* inhibitor capmatinib in Chinese adult patients with *EGFR* wild-type (wt), *ALK* rearrangement negative, *MET* exon 14 skipping mutations, advanced non-small cell lung cancer (NSCLC) who are treatment naive or failed one or two prior lines of systemic therapy
Brief title	Study of efficacy and safety of capmatinib in Chinese patients with *EGFR* wild-type (wt), *ALK* rearrangement negative, *MET* exon 14 skipping mutations, advanced NSCLC
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This phase II study is designed to support capmatinib new drug application (NDA) in China as a monotherapy in patients with *MET* mutated, advanced/metastatic NSCLC who are treatment naive (cohort 1) or failed one or two prior lines of systemic therapy (cohort 2).
Primary Objective(s)	The primary objective is to evaluate the antitumor activity of capmatinib, as measured by overall response rate (ORR) by blinded independent review committee (BIRC) assessment per RECIST 1.1, by cohort.
Secondary Objectives	The secondary objectives are the following: • To evaluate duration of response (DOR) as assessed by BIRC per RECIST 1.1, by cohort • To evaluate ORR and DOR by Investigator assessment per RECIST 1.1, by cohort • To evaluate time to response (TTR), disease control rate (DCR) and progression-free survival (PFS) by Investigator and by BIRC assessment per RECIST 1.1, by cohort • To evaluate overall survival (OS), by cohort • To assess intracranial anti-tumor activity of capmatinib in participants with Central Nervous System (CNS) lesions at baseline by BIRC by evaluating overall intracranial response rate (OIRR), intracranial disease control rate (IDCR), time to intracranial response (TTIR), duration of intracranial response (DOIR) by BIRC as per RANO-BM criteria • To evaluate the association between *MET* mutation status as measured in circulating tumor Deoxyribonucleic Acid (ctDNA) at baseline with capmatinib efficacy by evaluating ORR, DOR and PFS per RECIST 1.1 for participants by *MET* mutation status assessed in ctDNA at baseline, both by BIRC and Investigator • To characterize the pharmacokinetics (PK) of capmatinib by evaluating the steady state Ctrough and steady state 0.5-1.5 hour and 3-5 hours post-dose concentrations • To evaluate capmatinib safety profile by assessing the incidence of adverse events (AEs) and serious adverse events (SAEs), change in vital signs, laboratory results (hematology, chemistry, and urinalysis) and ECG • To assess the effect of capmatinib on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL) by evaluating the change from baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and Lung Cancer 13 (LC13), EuroQoL-5 Dimension-5 Level (EQ-5D-5L) • To assess the effect of capmatinib on patient-reported symptoms of brain metastases by evaluating the change from baseline to each visit in symptoms of brain metastases, with the NCCN FACT-FBrSI

Study design	This is an open-label, multicenter two-cohort phase II study. Cohort 1 will include treatment naive participants and Cohort 2 participants who failed one or two prior lines of therapy in the advanced stage (stage IIIB, IIIC or IV).
Study population	Approximately 35 Chinese adult participants with *EGFR* wt (*EGFR* mutations that predict sensitivity to *EGFR* therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations), *ALK* rearrangement negative, advanced (stage IIIB, IIIC or IV) NSCLC disease harboring *MET* exon 14-skipping *(MET*Δex14) mutations as determined by a Novartis central molecular laboratory will be treated in this study. The 1L cohort includes approximately 15 participants and 2/3L cohort includes approximately 20 participants.

Key Inclusion criteria	• Chinese adult ≥ 18 years old at the time of informed consent
	• Histologically confirmed stage IIIB, IIIC or IV NSCLC at the time of study entry, not amenable to curative surgery or radiation or multi-modality therapy
	• Histologically or cytologically confirmed diagnosis of NSCLC that is:
	  • *EGFR* wt: The *EGFR* wt status (*EGFR* mutations that predict sensitivity to *EGFR* therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations) must be documented in the participant source documents before the participant can be consented for pre-screening for *MET*Δex14 mutation status
	  • AND *ALK* rearrangement negative: The *ALK* rearrangement negative status must be documented in the participant source documents before the participant can be consented for pre-screening for *MET*Δex14 mutation status
	  • AND either:
	  • Cohort 1: Treatment naive participants with *MET*Δex14 mutations, or
	  • Cohort 2: Pre-treated participants with *MET*Δex14 mutations
	• Cohort 1: participants must not have received any systemic therapy for advanced/metastatic disease (stage IIIB, IIIC or IV NSCLC). Neo-adjuvant and adjuvant systemic therapies will not count as one prior line of treatment if relapse occurred > 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.
	• Cohort 2: participants must have failed one or two prior lines of systemic therapy for advanced/metastatic disease (stage IIIB, IIIC or IV NSCLC). Treatment failure is defined as documented disease progression or intolerance to treatment. Maintenance therapy given after first line chemotherapy will be considered as part of the first line if given to participants with documented response or stable disease before starting the maintenance therapy. Neoadjuvant and adjuvant systematic therapies will count as one prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.
	• At least one measurable lesion according to response evaluation criteria in solid tumors (RECIST) v1.1. Any lesions which have been subjected to percutaneous therapies or radiotherapy should not be considered measurable, unless the lesion has clearly progressed since the procedure.

Key Exclusion criteria	• Prior treatment with any *MET* inhibitor or HGF-targeting therapy. • Participants with known hypersensitivity to any of the excipients of capmatinib (i.e. crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes). • Participants with known druggable molecular alterations (such as *ROS1* translocation or *BRAF* mutation, etc.) which might be a candidate for alternative targeted therapies as applicable per local regulations and treatment guidelines.

	• Participants 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. If participants are treated with corticosteroids for endocrine deficiencies or tumor-associated symptoms other than CNS related, dose must have been stabilized (or decreasing) for at least 5 days before first dose of capmatinib. • Presence or history of carcinomatous meningitis. • Presence 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. • Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis affecting activities of daily living (ADL) or requiring therapeutic intervention.
Study treatment	Capmatinib (INC280)
Efficacy assessments	• Tumor assessment by RECIST 1.1 performed at screening/baseline and then every 6 weeks (+/- 7 days) from Cycle 3 Day 1 with capmatinib until disease progression as determined by Investigator and confirmed by BIRC. Participant who continues on study treatment beyond RECIST-defined PD (determined by Investigator and confirmed by BIRC) will continue to have tumor assessments as per regular visit schedule. • CNS lesions assessed by BIRC based on Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. • Survival status collected every 12 weeks regardless of treatment discontinuation reason (except if consent is withdrawn or participant is lost to follow-up) until death, lost to follow-up, or withdrawal of consent for survival follow-up.
Pharmacokinetic assessments	The following PK blood samples for capmatinib will be collected for all participants: Cycle 2 Day 1, pre-dose Cycle 2 Day 1, anytime within 0.5-1.5 hour post-dose Cycle 2 Day 1, anytime within 3-5 hours post-dose Cycle 3 Day 1, pre-dose
Key safety assessments	• Laboratory assessments including hematology, chemistry, coagulation and urinalysis • Physical examination • Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) • Vital signs and body weight • Electrocardiogram (ECG) • Collection of AEs and SAEs
Other assessments	• Patient Reported Outcomes (PRO): EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L and NCCN FACT-FBrSI
Data analysis	**Primary endpoint** The primary endpoint is the ORR by cohort as per the blinded independent review committee (BIRC) review. ORR is defined as the proportion of participants with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1. The primary analysis will be performed using full analysis set (FAS). The primary efficacy endpoint ORR will be estimated and the exact 95% confidence interval (CI) (Clopper and Pearson 1934) will be provided by cohort. **Secondary endpoints**

	Duration of response (DOR): DOR only applies to participants whose BOR is complete response (CR) or partial response (PR) according to RECIST 1.1 based on tumor response data. The start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to any cause. DOR will be assessed as per BIRC review and by Investigator assessment for FAS. Participants continuing without progression or death due to any cause will be censored at the date of their last adequate tumor assessment. **ORR by Investigator assessment:** The evaluation of ORR will be also conducted based on Investigator assessment. ORR will be estimated and the exact binomial 95% CI will be provided by cohort. **Time to Response (TTR):** TTR is defined as the time from the date of start of study drug to the first documented response of either complete response (CR) or partial response (PR), which must be subsequently confirmed (although date of initial response is used, not date of confirmation). TTR will be evaluated as per BIRC and also by Investigator review and according to RECIST 1.1. **Disease control rate (DCR)**: DCR is defined as the proportion of participants with a BOR of complete response (CR), or partial response (PR), or an overall response of stable disease (SD). DCR will be assessed as per BIRC as well as Investigator assessment according to RECIST 1.1. DCR and its 95% exact confidence interval will be presented for each cohort using FAS. **Progression-free survival (PFS**): PFS is defined as the time from the date of first dose of capmatinib to the date of the first documented progression according to RECIST 1.1, or death due to any cause. If a participant has no progression or death, the participant is censored at the date of last adequate tumor assessment. The analysis of PFS will be performed as per BIRC and per Investigator review. **Overall survival (OS):** OS is defined as the time from date of first treatment to date of death due to any cause. If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date). All time to event (TTE) variables (DOR, TTR, PFS, OS) distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, and 95% confidence intervals of the medians (in months) along with 25th and 75th percentile will be presented for each cohort using FAS. **Overall intracranial response rate (OIRR):** OIRR is calculated based on response assessments in the brain for participants having measurable and/or non-measurable brain metastases at baseline. OIRR is the proportion of participants with a confirmed best overall intracranial response (BOIR) of CR or PR per RANO-BM criteria as assessed by BIRC review. OIRR calculated based on the data from the FAS-BM and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented by cohort. **Intracranial disease control rate (IDCR):** IDCR is calculated based on response assessments in the brain for participants having measurable and/or non-measurable brain metastases at baseline. IDCR is the proportion of participants with a confirmed BOIR of CR or PR or SD (or non-CR/non-PD) per RANO-BM criteria as assessed by BIRC review. IDCR calculated based on the data from the FAS-BM and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented by cohort. **Time to intracranial response (TTIR)**: TTIR is defined as the time from the date of the start of study treatment to the date of the first documented intracranial response of either CR or PR per RANO-BM criteria as assessed

	by the BIRC review, which must be subsequently confirmed (date of initial response is used, not date of confirmation). Participants without a confirmed intracranial CR or PR will be censored at the study-maximum follow-up time (i.e. LPLV−FPFV) for participants with an intracranial PFS event (intracranial progression or death due to any cause), or at the date of the last adequate tumor assessment in brain for participants without an intracranial PFS event. All participants in the FAS-BM will be included in TTIR calculations. Median TTIR with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. TTIR will be summarized using the Kaplan-Meier (KM) method, based on data from the FAS-BM. KM estimates for TTIR proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided. **Duration of intracranial response (DOIR):** DOIR only applies to participants whose BOIR is CR or PR per RANO-BM criteria as assessed by BIRC review. DOIR is defined as the time from the date of first documented intracranial response of either CR or PR to the date of first documented intracranial progression per RANO-BM criteria or the date of death due to any cause. DOIR will be summarized using the KM method. Median DOIR, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for DOIR proportions at specific timepoints, along with95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided. The Pharmacokinetic Analysis Set (PAS) will be used in all pharmacokinetic data analysis and PK summary statistics. Descriptive summary statistics of plasma concentration will be provided by cohort and by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), Standard Deviation, coefficient of variation (CV)% (arithmetic and geometric), median, minimum and maximum. Evaluation of capmatinib safety profile will be performed by analyzing safety data such as AEs, ECG, vital and laboratory data. The association between *MET*Δex14 mutation status as measured in ctDNA at baseline with ORR, DOR and PFS will be established using Kaplan-Meier curve, by cohort separately provided the number of participants be considered large enough. Median survival together will their 95% confidence intervals will be reported. 95% CI will be generated for ORR using Fisher exact test. Descriptive statistics for continuous data will be used to summarize EORTC QLQ-C30/LC13, EQ-5D-5L, and NCCN FACT-FBrSI scores at each scheduled assessment time point by FAS. The scores will be displayed as mean profiles by cohort/sub-cohort, presented over time. The number of participants completing the questionnaires and the number of missing or incomplete assessments will be summarized for each scheduled assessment time point.
Key words	INC280, capmatinib, *MET*, NSCLC

1 Introduction

1.1 Background

Lung cancer is the most common cancer type worldwide, with an estimated 2.1 million new cases in 2018, representing 11.6% of all new cancers. It is also the most common cause of death from cancer, with 1.8 million deaths representing 18.4% of the total deaths from cancer (Bray et al 2018). In China, lung cancer is both the most common cancer and the most leading cause of cancer-related deaths. There were 733,300 new cases of lung cancer (85.0% were non-small cell lung cancer) and 610,200 patients died of lung cancer in China in 2015 (Chen et al 2016).

Mechanisms of oncogenesis in lung cancer have been largely deciphered over the past 20 years. Epidermal Growth Factor Receptor (*EGFR)* mutations, Anaplastic Lymphoma Kinase (*ALK)* translocations and Proto-oncogene tyrosine-protein kinase Reactive Oxygen Species (*ROS1)* rearrangements in NSCLC have approved targeted therapies in China (CSCO guidelines for primary lung cancer,2019). Besides these well-established oncogenic drivers, Mesenchymal Epithelial Transition (*MET)* is recognized as a promising molecular target. *MET* is a tyrosine kinase receptor and *MET* pathway can be dysregulated by several mechanisms including *MET* mutation, gene amplification, overexpression, and autocrine/paracrine stimulation by its ligand Hepatic Growth Factor (HGF) (Birchmeier et al 2003, Comoglio et al 2018). Activated *MET* promotes tumor cell growth, survival, invasion and metastasis, as well as tumor angiogenesis, resulting in poor clinical outcomes (Christensen et al 2005, Liu X et al 2008). *MET* exon 14 skipping mutations (*MET* mutated or *MET*ex14 mutated thereafter) remove the juxtamembrane domain of *MET*, leading to protein stabilization and oncogenic activation (Kong-Beltran et al 2006, Togashi et al 2015, Lu et al 2017). Globally, *MET* mutations leading to exon 14 skipping have been reported in 2-3% of NSCLC with adenocarcinoma histology and in ~1% of NSCLC with other histologies; notably no overlap between *MET* mutations and either *EGFR* mutations or *ALK* translocation is expected (TCGA Research Network 2014, Awad et al 2016, Tong et al 2016, Ou et al 2016). In China, it is reported as a rare alteration in 0.4-1.3% (Liu SY et al 2016, Zheng et al 2016, Wen et al 2019, Zhu et al 2019) of Chinese NSCLC patients.

Chinese Society of Clinical Oncology (CSCO) guidelines recommend platinum-doublet chemotherapy as first-line standard of care and single agent chemotherapy as second-line standard of care for treatment of advanced/metastatic NSCLC (CSCO guidelines for primary lung cancer, 2019) who are *EGFR*, *ALK* and *ROS1* negative. Outcomes of chemotherapies in both first-line setting with standard platinum-doublet chemotherapy (with or without maintenance treatment) and second-line setting with single agent remain poor. For locally advanced/metastatic NSCLC in the treatment naive setting, chemotherapy observed a median progression-free survival (PFS) of 5-7 months and overall survival (OS) of 10-16 months (Scagliotti et al 2008, Ciuleanu et al 2009, Ettinger et al 2010, Paz-Ares et al 2012). For pre-treated setting, the reported response rates to second-line chemotherapy also with other single agent chemotherapeutics have generally been < 11% with median PFS and OS generally below 4 and 11 months, respectively (de Marinis and Grossi 2008, Weiss and Stinchcombe 2013). Besides, Chinese *MET* mutant patients are characterized as elderly compared with the unselected NSCLC patient population (Zheng et al 2016). Treatment with chemotherapy is challenging in such a patient population limiting the available treatment options.

Treatment landscape for advanced NSCLC has been reshaped by immunotherapy which is now an established treatment option both in the pre-treated and in the treatment naive setting as single agent. In China, two immunotherapies (Programmed cell Death protein 1 [PD-1] inhibitors [nivolumab, pembrolizumab]) have been approved recently. On 15-Jun-2018 nivolumab was approved in the pre-treated setting of *EGFR* wt and *ALK*-negative advanced NSCLC. ORR (overall response rate) is 16.6% (nivolumab) vs 4.2% (docetaxel) in Checkmate-078 study (mainly Chinese), with median OS of 12.0 months vs 9.6 months (Hazard Ratio [HR] 0.68 (97.7% Confidence Interval [CI]: 0.52-0.90)) and median PFS of 2.8 months vs 2.8 months (HR 0.77 (95% CI: 0.62-0.95) (Wu et al 2019). On 28-Mar-2019 pembrolizumab plus pemetrexed+cisplatin was approved in first-line EGFR wt and ALK negative non-squamous advanced NSCLC. Several PD-1/Programmed Death-Ligand 1 (PD-L1) therapies are under clinical development in NSCLC with non-oncogenic drivers. However, to date, efficacy to immunotherapy in lung cancer patients harboring a *MET* exon 14 skipping (*MET*Δex14) alteration is still limited. Recent preliminary data showed that, similar to *EGFR*-mutated and *ALK*-translocated NSCLCs, patients with *MET* mutated NSCLC do not seem to benefit from treatment with immunotherapy (Sabari et al 2018, Awad et al 2019).

Promising efficacy data have also been seen in patients with *MET* mutated NSCLC treated with *MET* inhibitors, including capmatinib (Frampton et al 2015, Jenkins et al 2015, Mendenhall and Goldman 2015, Paik et at 2015, Waqar et al 2015, Liu X et al 2016, Schrock et al 2016, Awad et al 2019, Wolf et al 2019, Drilon et al 2020).

Capmatinib is a small adenosine triphosphate (ATP) competitive, orally bioavailable, highly potent, and selective reversible inhibitor of the *MET* receptor tyrosine kinase (Liu X et al 2011, Baltschukat et al 2019). GEOMETRY mono-1 [CINC280A2201], a phase II study in *MET* dysregulated NSCLC to treat capmatinib, reported its efficacy and safety data in *MET* mutated cohorts. Capmatinib achieved a 40.6% ORR (95% CI: 28.9-53.1) in 2/3L cohort and 67.9% (95% CI: 47.6-84.1) in 1L cohort by blinded independent review committee (BIRC) assessment. Median duration of response (DOR) per BIRC is 9.72 months in 2/3L cohort and 11.14 months in 1L cohort (Wolf et al 2019).

Currently, there is no approved targeted therapy for patients with *MET*Δex14 mutated NSCLC in China. *MET* mutation defines a distinct subset of Chinese NSCLC patients characterized by female, non-smoker, and older age (Zheng et al 2016). Available treatment options are very limited as introduced above. Considering tolerability of chemotherapy in elderly patients and limited unknown efficacy response to immunotherapy, a *MET* inhibitor, capmatinib, is needed to be developed in Chinese NSCLC harboring *MET* exon 14 mutation.

1.1.1 Overview of capmatinib (INC280)

1.1.1.1 Non-clinical experience

Capmatinib possesses potent inhibitory activity against the *MET* kinase in vitro [inhibitory concentration $(IC)_{50}$ = 0.6 nM], and is highly specific for *MET* with approximately 1,000 times or greater selectivity when compared to more than 400 other kinases or mutant kinase variants (Fujino et al 2019). Potent activity of blocking *MET* activation has been observed in cell-based biochemical and functional assays that measure *MET*-mediated signal transduction, as well as *MET*-dependent cell proliferation, survival, and migration.

In *MET*-dependent, mouse tumor models (including lung cancer models), capmatinib exhibits dose-dependent antitumor activity and causes tumor regression at well-tolerated doses that exceeded IC_{90} coverage (Liu X et al 2011). Importantly, plasma levels of capmatinib correlate with both the dose administered and the extent of tumor growth inhibition in vivo.

In *MET*/HGF-driven tumor models grown as xenografts in mice, oral dosing of capmatinib demonstrated significant in vivo activity in blocking both *MET* phosphorylation and tumor growth. Activation of *MET* in such responsive models is either due to strong *MET* overexpression (mostly because of gene amplification, e.g. in gastric or hepatocellular carcinoma) or HGF secretion resulting in an autocrine loop (e.g. in glioblastoma).

For further details, please refer to the latest version of the [capmatinib Investigator's Brochure].

1.1.1.2 Clinical experience

Capmatinib has been extensively tested in both healthy volunteers and cancer patients. As of the safety cut-off date of 27-Sep-2019, more than 780 participants with solid tumors have been treated with capmatinib as a single agent, and more than 690 participants have received capmatinib in combination with other therapies. The recommended phase II dose (RP2D) for capmatinib as a single agent has been determined to be 400 mg twice daily (b.i.d.) in tablet formulation [capmatinib Investigator's Brochure].

The most frequent adverse events (AEs) suspected to be related to capmatinib of any grade reported in study [CINC280A2201], reference study for the safety profile of capmatinib monotherapy (n=334), across study cohorts and irrespective of *MET* mutational status, were edema peripheral (41.6%), nausea (33.2%), blood creatinine increased (19.5%), vomiting (18.9%), fatigue (13.8%), decreased appetite (12.6% and diarrhea (11.4%) and the majority were Grade 1/2. The Grade 3/4 AEs suspected to be related to capmatinib in the [CINC280A2201] study included edema peripheral (7.5%) and lipase increased (5.1%), alanine aminotransferase increased (4.8%), amylase increased (3.0%), fatigue (3.0%), aspartate aminotransferase increased (2.4%), nausea and vomiting (1.8%), decreased appetite (0.9%), constipation (0.6%), and diarrhea (0.3%) [capmatinib Investigator's Brochure].

Efficacy data for capmatinib single agent in previously treated patients with locally advanced or metastatic NSCLC harboring *MET* 14 exon skipping mutation have been reported in the group 4 of phase II GEOMETRY 1 study [CINC280A2201]: as of 15-Apr-2019, RECIST 1.1 confirmed major responses (including a complete response) evaluated by BIRC were observed in 28 out of 69 (ORR 40.6%, [95% CI: 28.9-53.1]) evaluable patients (defined as those with at least one post-baseline tumor assessment or have discontinued treatment at the time of the data cut-off) and median DOR was 9.72 months [95% CI: 5.55-12.98]. Median PFS was 5.42 months [95% CI: 4.17-6.97]. Moreover, major intracranial responses were observed in 7 out of 13 evaluable patients with brain metastasis at baseline. Four patients had complete resolution of lesion (Wolf et al 2019). Based on these data, capmatinib received breakthrough therapy designation for treatment of treatment naive and pre-treated NSCLC patients with *MET*Δex14 mutations from the United States (US) Food and Drug Administration (FDA). FDA also granted an orphan drug designation to capmatinib for treatment of patients with *MET* dysregulated NSCLC.

Pharmacokinetics (PK) data collected in clinical trials showed that capmatinib is rapidly absorbed after oral administration with a median time to reach maximum drug concentration (T_{max}) ranging from 1 to 2 hours for tablets. The elimination half-life estimated from study [CINC280X1101] ranged from 3.5 to 6.3 hours across the cohorts. Steady state is achieved by day 3 of 400 mg twice daily dosing. Accumulation in capmatinib exposure following repeated administration of 400 mg b.i.d. tablets is low, with geometric mean accumulation ratio of 1.39-fold in the single agent [CINC280A2201] study. The mean plasma exposure increase is roughly dose proportional for capmatinib tablet from 200 to 400 mg b.i.d..

The PK and safety of capmatinib administered with food has been evaluated in cancer patients in study [CINC280A2108]. No significant difference in exposure was seen when capmatinib was given under fasted conditions or with food. The safety profile was similar to that of study [CINC280A2201], with no dose-limiting toxicities (DLTs) observed. Given the above, capmatinib may be administered with or without food.

Capmatinib is a moderate Cytochrome P450 1A2 (CYP1A2) inhibitor [CINC280A2103] and an inhibitor of Permeability-GlycoProtein (P-gp) and Breast Cancer Resistance Protein (BCRP) transporter [CINC280A2105]. Therefore, CYP1A2 substrates, P-gp substrates, and BCRP substrates where minimal concentration changes may lead to serious adverse reactions should be avoided. If co-administration is unavoidable, decrease the dosage of CYP1A2 substrates, P-gp substrates, or BCRP substrates in accordance with the approved prescribing information.

When co-administered with the strong Cytochrome P450 3A (CYP3A) inhibitor itraconazole, capmatinib Area Under Curve (AUC) increased by approximately 42% without any change in Maximum (peak) concentration of drug in plasma (C_{max}). When co-administered with the strong CYP3A inducer rifampicin, capmatinib AUC and C_{max} decreased by 67% and 56%, respectively [CINC280A2102]. Hence, adverse reactions during co-administration of capmatinib with strong CYP3A inhibitors should be closely monitored, in addition, strong CYP3A inducers should be avoided in participants treated with capmatinib.

For further details, please refer to the latest version of the [capmatinib Investigator's Brochure].

1.2 Purpose

This phase II registration China alone study will assess efficacy and safety of capmatinib in Chinese participants to support capmatinib new drug application (NDA) in China as a monotherapy in patients with *MET* mutated, advanced/metastatic NSCLC who are treatment naive or failed one or two prior lines of systemic therapy.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoints for primary objective**
• To evaluate the antitumor activity of capmatinib, as measured by overall response rate (ORR) by blinded independent review committee (BIRC) assessment, by cohort	• ORR, proportion of participants with a best overall response (BOR) defined as complete response or partial response (CR+PR) by BIRC assessment per RECIST 1.1
Secondary objectives	**Endpoints for secondary objectives**

Objectives	Endpoints
• To evaluate duration of response (DOR) as assessed by BIRC, by cohort	• DOR, calculated as the time from the date of the first documented CR or PR by BIRC per RECIST 1.1 to the first documented progression or death due to any cause for participants with PR or CR
• To evaluate ORR and DOR by Investigator assessment, by cohort	• ORR (CR+PR) and DOR per RECIST 1.1 by Investigator assessment
• To evaluate time to response (TTR), disease control rate (DCR) and progression-free survival (PFS) by Investigator and by BIRC assessment, by cohort	• All calculated per RECIST 1.1, both by BIRC and Investigator: • TTR, calculated as the time from first dose of capmatinib to first documented response (CR+PR) for participants with PR or CR • DCR, calculated as the proportion of participants with BOR of CR, PR, or SD • PFS, defined as time from first dose of capmatinib to progression or death due to any cause
• To evaluate overall survival (OS), by cohort	• OS, defined as time from first dose of capmatinib to death due to any cause
• To assess intracranial anti-tumor activity of capmatinib in participants with Central Nervous System (CNS) lesions at baseline by BIRC	• Overall intracranial response rate (OIRR), intracranial disease control rate (IDCR), time to intracranial response (TTIR), duration of intracranial response (DOIR) by BIRC as per RANO-BM criteria
• To evaluate the association between *MET*Δex14 mutation status as measured in ctDNA at baseline with capmatinib efficacy	• ORR, DOR and PFS per RECIST 1.1 for participants by METΔex14 mutation status assessed in ctDNA at baseline, both by BIRC and Investigator
• To characterize the pharmacokinetics of capmatinib	• Steady state Ctrough and steady state 0.5-1.5 hour and 3-5 hours post-dose concentrations
• To evaluate capmatinib safety profile	• Incidence of adverse events (AEs) and serious adverse events (SAEs), change in vital signs, laboratory results (hematology, chemistry, and urinalysis) and ECG
• To assess the effect of capmatinib on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL)	• Change from baseline in European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and LC13, EuroQoL-5 Dimension-5 Level (EQ-5D-5L)
• To assess the effect of capmatinib on patient-reported symptoms of brain metastases	• Change from baseline to each visit in symptoms of brain metastases, with the NCCN FACT-FBrSI

2.1 Primary estimands

The primary scientific question of interest is: what is the effect of capmatinib in inducing radiological response in Chinese participants with *MET*Δex14 mutation, regardless of study treatment discontinuation and prior to start of new antineoplastic therapy?

The primary estimand will be described by the following five attributes:

1. The population is the adult Chinese participants with *EGFR* wild-type (wt), *ALK* rearrangement negative, *MET* exon 14 skipping mutations advanced non-small cell lung cancer (NSCLC) who are either treatment naive or failed one or two prior lines of systemic therapy
2. The treatment attribute is the oral dose of capmatinib 400 mg administered twice daily (b.i.d.) i.e. total dose of 800 mg daily

3. The variable is the best overall response (BOR) defined as the best response recorded from the date of treatment start until disease progression/recurrence (taking as reference for PD, the smallest measurement recorded since the treatment started) based on BIRC per RECIST 1.1. prior to start of any antineoplastic therapy
4. The intercurrent events of interest are:
   a. The treatment discontinuation for any reason: tumor assessment data collected irrespectively of treatment discontinuation will be included to derive BOR (treatment strategy)
   b. Start of antineoplastic therapy: if any antineoplastic therapy is taken and any response after the antineoplastic therapy will be considered as non-responder (composite strategy)
   c. Any public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster: assessment collected irrespectively of those events will be included to derive BOR (treatment policy strategy)
5. The summary measure is the overall best overall response rate (ORR) and its exact 95% confidence interval (CI) (Clopper and Pearson 1934) will be provided by cohort.

2.2 Secondary estimands

Not applicable.

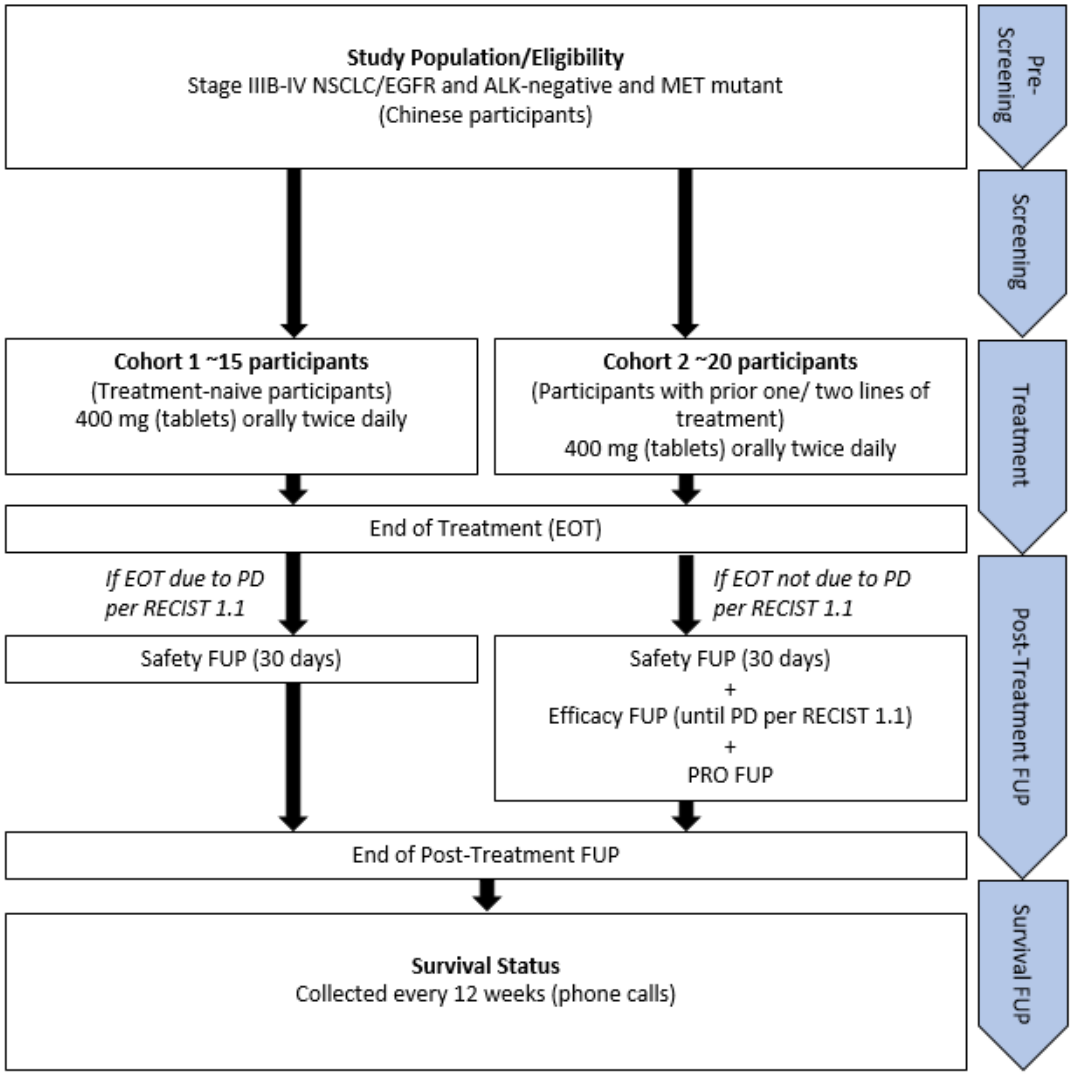
3 Study design

This is an open-label, multicenter two-cohort phase II study to evaluate the efficacy and safety of single-agent capmatinib in Chinese participants with *EGFR* wt (*EGFR* mutations that predict sensitivity to *EGFR* therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations), *ALK* rearrangement negative, *MET* exon 14 skipping mutated advanced/metastatic NSCLC.

Approximately 35 participants aged 18 or over will be treated in this study in two separate cohorts. Cohort 1 will include approximately 15 treatment naive participants and Cohort 2 approximately 20 participants who failed one or two prior lines of therapy in the advanced stage (refer to Section 12.8.1). Each participant will receive 400 mg capmatinib tablet b.i.d..

Refer to Figure 3-1 for an overview of the study design.

Figure 3-1 Study design



Pre-Screening:

Participants must sign a Molecular Pre-Screening Informed Consent Form (ICF) prior to any study specific molecular pre-screening evaluations.

In order to be considered eligible for the study, participants must have *MET*Δex14 mutation confirmed by a Novartis-designated central laboratory (refer to Section 8.1).

A Subject Number (Subject No.) will be assigned to each participant and the Investigator or designated staff will provide the requested identifying information to register the participant in the Interactive Response Technology (IRT) system.

Screening:

Participants must sign an Informed Consent Form (ICF) prior to any study specific screening evaluations and as early as 28 days prior to the start of study treatment.

Following completion of all required screening procedures (refer to Section 8.2) and verifying participant eligibility, the Investigator or designated staff will confirm participant eligibility in IRT system.

Treatment:

Study treatment will begin on Cycle 1 Day 1 with the first administration of study treatment. Participants will continue treatment until reasons for discontinuation of study treatment are met (Section 9.1.1).

Participants will be evaluated radiologically at screening/baseline then every 6 weeks to assess treatment response until PD by RECIST 1.1 as assessed by the Investigator and confirmed by BIRC.

An end of treatment (EOT) visit will be performed when participants permanently discontinue study treatment.

Post-treatment Follow-Up (FUP) (Safety, Efficacy and PRO Follow-Up):

After treatment discontinuation, all participants will be followed for safety evaluations as outlined in details in Section 6.5.2 and Section 9.3.1 during the safety follow-up period. Participants will be followed for safety up to 30 days after the last dose of study drug. If a new antineoplastic therapy is initiated after study treatment, safety follow-up will focus on events suspected to be related to study treatment only.

In addition to the 30-day safety follow-up, participants who discontinue study treatment without prior documented PD, will continue efficacy assessments (Efficacy Follow-up) during the post-treatment follow-up until documented PD by RECIST 1.1 as assessed by the Investigator and confirmed by BIRC, participant withdrawal of consent, physician's decision, lost to follow-up, death, or study is terminated by the sponsor as outlined in Section 8.4.1.4 and Section 9.3.2. For these participants, participants-reported outcomes (PRO) will also continue to be collected electronically (PRO Follow-up) until documented progression.

Survival Follow-up:

After study treatment discontinuation due to PD or post-treatment follow-up phase discontinuation due to other reasons except PD, the participant's survival status will be collected every 12 weeks (via phone calls) as part of the survival follow-up phase (Section 9.3.3).

Every effort should be made to comply with the survival follow-up schedule and ensure collection of participant survival data.

4 Rationale

4.1 Rationale for study design

Details on the rationale for the study design is described in the Table 4-1 below.

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Study population	The study will enroll Chinese adult patients with *EGFR* wt, *ALK* rearrangement negative, *MET* exon 14 skipping mutations, advanced NSCLC who are treatment naive or failed one or two prior lines of systemic therapy. Participants must be *MET* inhibitor naive. Participants with targetable oncogenic drivers (such as *EGFR*-sensitizing mutations, or *ALK* translocation) will be excluded as approved targeted therapies for such patients exist. For more details on study population, please refer to Section 5.
Single arm	This is a very rare patient population with high unmet medical need and with no previously conducted study globally with good efficacy and safety data. A single arm study is therefore justified and will satisfy the health authorities (HA) requirement for registration.
Two-cohort study	• Cohort 1: Treatment naive participants with *MET*Δex14 mutated NSCLC who did not receive any systemic therapy for advanced/metastatic disease. • Cohort 2: Pre-treated participants with *MET*Δex14 mutated NSCLC who failed one or two prior lines of systemic therapy for advanced/metastatic disease.
Comparator treatment	Not applicable.
Open-label	Not applicable.
Stratification factors	Not applicable.
Randomization	Not applicable.
Treatment beyond disease progression	This is to ensure those participants (in either cohort) who are clinically stable, tolerate the treatment, and are deriving clinical benefit can continue to receive treatment. Timely follow-up after the initial PD will ensure that participants with confirmed/rapid progression will be discontinued and can initiate adequate subsequent therapies.

4.2 Rationale for dose/regimen and duration of treatment

Based on the PK and safety data, capmatinib 400 mg b.i.d. in tablet formulation was declared to be the recommended phase II dose (RP2D) [CINC280X2102]. Furthermore, robust efficacy has been demonstrated in both 2/3L and 1L *MET* mutant NSCLC participants at this dose level [CINC280A2201]. In addition, sustained target coverage was expected at this dose as 96% of participants can maintain capmatinib plasma concentration above IC_{95} for *MET* inhibition during the dosing interval [Population PK report]. For further details, please refer to the latest version of the [capmatinib Investigator's Brochure].

CCI

[redacted]

CCI [redacted]

In this study, capmatinib 400 mg b.i.d. orally will be administered. Duration of treatment is continuous until disease progression or other reasons for drug discontinuation. Treatment with capmatinib may be continued beyond RECIST1.1-defined PD (as assessed by the Investigator and confirmed by BIRC) if considered by the Investigator to be in the best interest of the participant and as long as no new anticancer treatment is initiated.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

The participants enrolled in this study will have stage IIIB, IIIC (not amenable to surgery, radiation or multi-modality therapy) or stage IV NSCLC. Given the clinical and molecular characteristics of *MET*Δex14 mutated NSCLC, participants have fewer therapeutic options and the established standard of care has limited benefit in this patient population.

Capmatinib is one experimental treatment that has shown so far a manageable safety profile and clinically meaningful activity in this population (please refer to Section 1.1). Participants enrolled in the current study will have the possibility of receiving a potentially efficacious treatment for a currently unmet medical need.

The protocol includes specific eligibility criteria (Section 5), monitoring visits and assessments, dose modification and stopping rules, and recommended guidelines for treatment of expected toxicities, including identification and management of study-drug induced AEs. Recommended guidelines for prophylactic or supportive treatment of expected toxicities, including the management of study-drug induced AEs (e.g. infusion reaction, pneumonitis), are provided in Section 6.5.

The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as by close clinical monitoring and oversight. As with any clinical study, there may be unforeseen risks with the study treatment, which could be serious. The specific risks for capmatinib is discussed in Section 4.5.1. For further details, refer to the toxicity data provided in the current [capmatinib Investigator's Brochure].

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the

contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Therefore, the overall safety risk to participants enrolled in this study is considered manageable, based on the available clinical safety data for capmatinib, along with the eligibility criteria and monitoring measures implemented in this study.

4.5.1 Capmatinib

Based upon the clinical experience with capmatinib to date, the overall risk-benefit assessment of capmatinib is considered favorable. The data from study [CINC280A2201] show that capmatinib is generally well tolerated and has a manageable safety profile. The safety profile in the *MET*Δex14 mutated NSCLC population is consistent with the safety profile of capmatinib across multiple clinical studies.

The most frequent adverse events (AEs) on treatment with capmatinib monotherapy include peripheral edema, nausea, increased blood creatinine, vomiting, fatigue, decreased appetite, and diarrhea.

In addition, pancreatic events (e.g. amylase and lipase increase), and liver function test (LFT) alterations (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) and/or bilirubin increase) have been observed in participants treated with capmatinib. To date, a direct toxic effect of capmatinib on pancreas cannot be definitively identified. Caution is recommended when capmatinib is administered in combination with other drugs with a known risk of hepatotoxicity.

Pneumonitis and Interstitial Lung Disease (ILD) have been reported from both capmatinib single agent and combination studies with *EGFR* tyrosine kinase inhibitors (TKIs), including events with fatal outcomes. Investigators are advised to carefully monitor participants for signs and symptoms of pneumonitis and implement dose modification and follow-up evaluations described in the protocol in all capmatinib studies, both single agent and in combination studies.

Finally, capmatinib has shown photosensitization potential in in vitro and in vivo assays. The Investigators should recommend the use of precautionary measures against ultraviolet exposure to the participants during treatment with capmatinib (e.g. use of sunscreen, protective clothing and avoid sunbathing or using a solarium intensively).

For further information on potential toxicities, please refer to the current [capmatinib Investigator's Brochure].

4.6 Rationale for Public Health Emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

5 Study Population

Approximately 35 adult participants with *EGFR* wt (*EGFR* mutations that predict sensitivity to *EGFR* therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations), *ALK* rearrangement negative, advanced (stage IIIB, IIIC or IV, referencing CSCO guidelines for primary lung cancer, 2019) NSCLC disease harboring *MET*Δex14 mutations as determined by a Novartis central molecular laboratory will be treated in this study. The 1L cohort includes approximately 15 participants and 2/3L cohort includes approximately 20 participants.

Participants enrolled in the study are not permitted to participate in additional, parallel, investigational drug or device studies.

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

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Chinese adult ≥ 18 years old at the time of informed consent
3. Histologically confirmed stage IIIB, IIIC or IV NSCLC at the time of study entry, not amenable to curative surgery or radiation or multi-modality therapy (according to staging definition in CSCO guidelines for primary lung cancer, 2019).
4. Histologically or cytologically confirmed diagnosis of NSCLC that is:
   - *EGFR* wt: The *EGFR* wt status (*EGFR* mutations that predict sensitivity to *EGFR* therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations) must be documented in the participant source documents before the participant can be consented for pre-screening for *MET* mutation status
   - AND *ALK* rearrangement negative: The *ALK* rearrangement negative status must be documented in the participant source documents before the participant can be consented for pre-screening for *MET* mutation status
   - AND either:
     - Cohort 1: Treatment naive participants with *MET* mutations, or
     - Cohort 2: Pre-treated participants with *MET* mutations
5. Cohort 1: participants must not have received any systemic therapy for advanced/metastatic disease (stage IIIB, IIIC or IV NSCLC). Neo-adjuvant and adjuvant systemic therapies will not count as one prior line of treatment if relapse occurred > 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.

   Cohort 2: participants must have failed one or two prior lines of systemic therapy for advanced/metastatic disease (stage IIIB, IIIC or IV NSCLC). Treatment failure is defined as documented disease progression or intolerance to treatment. Maintenance therapy given after first line chemotherapy will be considered as part of the first line if given to participants with documented response or stable disease (SD) before starting the maintenance therapy. Neoadjuvant and adjuvant systematic therapies will count as one prior line of treatment if

relapse occurred within 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.

6. At least one measurable lesion according to RECIST v1.1. Any lesions which have been subjected to percutaneous therapies or radiotherapy should not be considered measurable, unless the lesion has clearly progressed since the procedure.
7. Participants must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (Common Terminology Criteria for Adverse Events (CTCAE) version 5.0). Participants with any grade of alopecia are allowed to enter the study.
8. Participants must have adequate organ function including the following laboratory values at the screening visit:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 109/L without growth factor support
   - Platelets (PLT) ≥ 75 x 109/L
   - Hemoglobin (Hgb) ≥ 9 g/dL
   - Calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 45 mL/min
   - Total bilirubin ≤ 1.5 x Upper Limit of Normal (ULN)
   - Aspartate transaminase (AST) ≤ 3 x ULN, except for participants with liver metastasis, who may only be included if AST ≤ 5 x ULN
   - Alanine transaminase (ALT) ≤ 3 x ULN, except for participants with liver metastasis, who may only be included if ALT ≤ 5 x ULN
   - Alkaline phosphatase (ALP) ≤ 5.0 x ULN
   - Asymptomatic serum amylase ≤ 5 x ULN (grade ≤ 2). Participants with grade 1 or grade 2 serum amylase at the beginning of the study must be confirmed to have no signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.)
   - Serum lipase ≤ ULN
9. ECOG performance status (PS) ≤1
10. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Prior treatment with any *MET* inhibitor or HGF-targeting therapy.
2. Participants with known hypersensitivity to any of the excipients of capmatinib (i.e. crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes).
3. Participants with known druggable molecular alterations (such as ROS1 translocation or BRAF mutation, etc.) which might be a candidate for alternative targeted therapies as applicable per local regulations and treatment guidelines.
4. Participants 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. If participants are treated with corticosteroids for endocrine deficiencies or tumor-associated symptoms other than CNS

related, dose must have been stabilized (or decreasing) for at least 5 days before first dose of capmatinib.

5. Presence or history of carcinomatous meningitis.
6. Presence 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.
7. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis affecting activities of daily living or requiring therapeutic intervention.
8. Concomitant medication(s) with a "Known Risk of Torsades de Pointes" per //.qtdrugs.org that cannot be discontinued or replaced by safe alternative medication.
9. Clinically significant, uncontrolled heart disease such as:
    - Unstable angina within 6 months prior to screening
    - Myocardial infarction within 6 months prior to screening
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening. If white coat syndrome (WHS) is suspected, blood pressure measurements may be repeated.
    - Ventricular arrhythmias
    - Supraventricular and nodal arrhythmias not controlled with medication
    - Other cardiac arrhythmia not controlled with medication
    - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or QT interval corrected by Fridericia's formula (QTcF) ≥ 470 ms on the screening ECG (as mean of triplicate ECG)
10. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting capmatinib or participants 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 capmatinib or participants who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting capmatinib is allowed.
11. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting capmatinib or who have not recovered from side effects of such procedure. Thoracoscopy for biopsy and mediastinoscopy will not be counted as major surgery and participants can be enrolled in the study ≥ 1 week after the procedure.
12. Participants receiving treatment with strong inducers of CYP3A and cannot be discontinued at least 1 week prior to the start of treatment with capmatinib and for the duration of the study.

13. Impairment of gastro-intestinal (GI) function or GI disease that may significantly alter the absorption of capmatinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
14. Unable or unwilling to swallow tablets as per dosing schedule.
15. Substance abuse, active infection (including active hepatitis B and C, participants whose disease is controlled under antiviral therapy are eligible, and human immunodeficiency virus (HIV) history positive) or other severe, acute, or chronic medical or psychotic 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.
16. Applicable to Cohort 2 only: Previous anti-cancer and investigational agents within 4 weeks or ≤ 5 x half-life of the agent (whichever is shorter) before first dose of capmatinib. If previous treatment is a monoclonal antibody, then the treatment must be discontinued at least 4 weeks before first dose of capmatinib. If previous treatment is an oral targeted agent, then the treatment must be discontinued at least 5 x half-life of the agent.
17. Pregnant or nursing (lactating) women.
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 7 days after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
    - Use of oral (estrogen and progesterone), 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 if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age-appropriate history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to enrollment on study. 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 to be not of child-bearing potential.

19. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 7 days after stopping study treatment. A condom is required for **all** sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.

    If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.
20. Participants who received live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, bacillus Calmette-Guerin (BCG), yellow fever, varicella, TY21a typhoid vaccines and live COVID-19 vaccines) within 30 days prior to the first dose of study treatment.

6 Treatment

6.1 Study treatment

For this study, the investigational drug is capmatinib. The drug will be labeled and provided to sites by Novartis in compliance with legal requirements in China.

6.1.1 Investigational drug

The study treatment begins on Cycle 1 Day 1 with the first administration of capmatinib. Cycle 1 Day 1 should occur on the day of confirmation of participant eligibility into the IRT system or no later than 3 days after this confirmation.

Capmatinib can be administered with or without food. The morning and the evening doses should be taken 12 (± 4) hours apart, although 12-hour interval is highly recommended. The morning dose should be taken the same time each morning. If a dose is not taken within 4 hours of the planned dosing time, the missed dose should not be replaced.

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Treatment Form or Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
Capmatinib (INC280) 150 mg or 200 mg	Film-coated tablet	Oral use	Open-label, participant specific bottles	Global

All doses prescribed and dispensed to the participants, and all dose changes during the study must be recorded on the appropriate electronic Case Report Form (eCRF). Refer to Section 6.7.2 for study drug prescribing and administration information and to Section 6.5.1 for dose modification information.

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.1.3 Treatment arms/group

Participants will be assigned to one of the following cohorts:

- Cohort 1: Treatment naive participants with *MET*Δex14 mutations
- Cohort 2: Pre-treated participants with *MET*Δex14 mutations

All participants, regardless of the cohort they belong to, will be treated with capmatinib as described below:

- Capmatinib 400 mg (tablets) orally b.i.d. with or without food
- Capmatinib will be given as continuous daily dosing, and the first dose is administered at the study center
- A complete cycle of treatment is defined as 21 days of continuous capmatinib treatment.

6.1.4 Guidelines for continuation of treatment

Participant should continue to receive the study treatment until one or more criteria for treatment discontinuation described in Section 9.1.1 are met.

Guidelines on the management of common capmatinib associated toxicities and dose modification instructions are provided in Section 6.5.1.

6.1.5 Treatment duration

Participants should continue to receive the study treatment until one or more criteria for treatment discontinuation described in Section 9.1.1 are met.

Participants may continue treatment beyond disease progression as per RECIST 1.1 criteria (as assessed by the Investigator and confirmed by BIRC) if, in the judgment of the Investigator, there is evidence of clinical benefit and the participant wishes to continue on the study treatment. Criteria for treatment beyond progression are described in Section 6.1.5.1.

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to participants who in the opinion of the Investigator are still deriving clinical benefit, where permitted by and in accordance with local laws and regulations.

6.1.5.1 Treatment beyond disease progression

Clinical data indicate that participants may derive benefit from continuing study treatment despite initial evidence of disease progression.

Participants treated with capmatinib will be permitted to continue study treatment beyond initial disease progression as per RECIST 1.1 criteria (as assessed by Investigator and confirmed by BIRC) provided they meet the following criteria:

- Evidence of clinical benefit assessed by Investigator
- No rapid radiological or clinical progression
- Tolerance to study treatment
- Should not jeopardize critical interventions to treat/prevent severe complications, or prevent participants from receiving adequate care
- Participant performance status is stable
- Participant wishes to continue on the study treatment

- No new antineoplastic therapy has been initiated

Participants who meet the above criteria and continue treatment beyond initial disease progression as per RECIST 1.1 will continue all study procedures as outlined in Section 8. In case of clinical deterioration or suspicion of further disease progression, a follow-up imaging assessment should be performed promptly rather than waiting for the next scheduled assessment.

Participants who are no longer deriving clinical benefit, or who meet other protocol discontinuation criteria must be discontinued.

6.2 Other treatment(s)

No additional treatment beyond investigational drug is provided in this trial.

6.2.1 Concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the participant are allowed except when specifically prohibited (see Section 6.2.2).

The participant must be told to notify the investigational site about any new medications he/she takes after signing the main study ICF. All medications (excluding the current study treatment), surgeries, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant signs the main study ICF and up to 30 days after the last dose of study drugs must be recorded on the appropriate eCRF. For participants with brain metastases at baseline, steroid use should be collected on the appropriate eCRF until disease progression (as determined by Investigator and confirmed by BIRC). Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications, food supplements and vitamins.

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to participants
- No anticancer agents other than the study medication should be given to participants.

Participants are permitted to use the following medications while taking study drug:

- Oral or topical antibiotics
- Medications to prevent or treat nausea, vomiting or diarrhea
- Growth factors (e.g. granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin, platelets growth factors, etc.) are allowed per the Investigator's judgement and per local guidelines.
- Oxygen therapy and blood products or transfusions
- Nutritional support or appetite stimulants
- Pain medication

CCI

CCI [redacted]

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The following medications should be used with caution when concomitantly used with capmatinib treatment in this study:

- Capmatinib is a moderate CYP1A2 inhibitor. Co-administration of capmatinib increased sensitive CYP1A2 probe substrate (caffeine) AUCinf by 134%. Avoid co-administration of capmatinib with CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions. If co-administration is unavoidable, decrease the CYP1A2 substrate dosage in accordance with the approved prescribing information.
- Co-administration of capmatinib increased P-gp substrate (digoxin) exposure (AUCinf and Cmax by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUCinf and Cmax by 108% and 204%, respectively). Avoid co-administration of capmatinib with P-gp and BCRP substrates where minimal concentration changes may lead to serious adverse reactions. If co-administration is unavoidable, decrease the P-gp or BCRP substrate dosage in accordance with the approved prescribing information.
- Co-administration of capmatinib with a strong CYP3A inhibitor (itraconazole) increased capmatinib AUCinf by 42%. There was no change in capmatinib Cmax. Closely monitor patients for adverse reactions during co-administration of capmatinib with strong CYP3A inhibitors.
- Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that coadministration of capmatinib with the moderate CYP3A inducer efavirenz (600 mg once daily for 20 days) would result in a 44% decrease in capmatinib AUC0-12h and 34% decrease in Cmax at steady-state compared to administration of capmatinib alone. Caution should be exercised during concomitant use of capmatinib with moderate CYP3A inducers. Use an alternative medication with no or minimal potential to induce CYP3A during coadministration with capmatinib.
- Co-administration of capmatinib with proton pump inhibitor (rabeprazole) decreased capmatinib AUCinf by 25% and Cmax by 38%. Exercise caution during concomitant use of capmatinib with proton pump inhibitors.
- As an alternative to proton pump inhibitors, an H2-receptor antagonist or antacid can be taken. Capmatinib should be administered at least 3 hours before or 6 hours after an H2-receptor antagonist. Capmatinib should be administered at least 2 hours before or 2 hours after an antacid.

Refer to Table 6-2 for a list of the medications that require caution when concomitantly used with capmatinib.

Table 6-2 Drugs to be used with caution during co-administration with capmatinib

Mechanism of Interaction	Drug Name
Strong CYP3A inhibitors	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, eltegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
CYP1A2 substrates with NTI	theophylline, tizanidine
Moderate CYP3A inducers	bosentan, dabrafenib, efavirenz, etravirine, genistein, modafinil, nafcillin, tipranavir/ritonavir, lopinavir, telotristat
P-gp substrates	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, atorvastatin, boceprevir, bosentan, carvedilol, caspofungin, ceritinib, colchicine, cyclosporine, dabigatran, digoxin, docetaxel, doxepin, doxorubicin, eribulin, everolimus, fentanyl, fexofenadine, fidaxomicin, fluvastatin, fosamprenavir, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, linagliptin, linezolid, loperamide, losartan, maraviroc, mirabegron, nadolol, naloxegol, nateglinide, nevirapine, nintedanib, olodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, proguanil, posaconazole, pravastatin, ranolazine, ritonavir, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
BCRP substrates	atorvastatin, daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitors	esomeprazole, pantoprazole, omeprazole, lansoprazole, rabeprazole, dexlansoprazole
H_2-receptor antagonists	cimetidine, famotidine, nizatidine, ranitidine
Antacids	aluminum hydroxide, aluminum carbonate, calcium hydroxide, calcium carbonate, bismuth subsalicylate
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, 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". This list may not be exhaustive and could be updated periodically. Please refer to the above links for latest information. NTI: narrow therapeutic index	

6.2.1.2 Use of bisphosphonates or RANKL inhibitor

Treatment with bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor for pre-existing bone metastases is permitted, if clinically indicated, and following existing guidelines in China. Treatment with bisphosphonates or RANKL inhibitor should preferably begin before the study treatment is initiated, but can also be initiated during therapy only if absence of radiological bone disease progression is well documented (in this case, the reason for its use must be clearly documented; i.e. "pre-existing, non-progressing, bone metastases").

6.2.1.3 Local radiotherapy

Localized palliative radiotherapy for pre-existing, painful bone/liver metastases is permitted. Local bone radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. It should not be delivered to a target lesion. 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 ruled out. The study treatment must be interrupted on the days of radiotherapy and can be resumed the day after its completion. Caution is advised for radiation to fields that include lung tissue. The radiotherapy must be listed on the concomitant antineoplastic therapy – radiotherapy eCRF. After documented progression by RECIST 1.1, radiotherapy is allowed following the same dose adjustment guidance in case capmatinib is continued beyond PD.

6.2.2 Prohibited medication

During the course of the study, participants must not receive other antineoplastic therapies (e.g. investigational drugs, devices, chemotherapy, immunotherapies) or any other therapies that may be active against cancer.

There are no prohibited therapies during the post-treatment follow-up period.

During the treatment period, co-administration of capmatinib with a strong CYP3A inducer (rifampicin) decreased capmatinib AUC_{inf} by 67% and C_{max} by 56% Table 6-3 which may decrease capmatinib anti-tumor activity. Therefore, concurrent use of strong CYP3A inducers are prohibited [capmatinib Investigator's Brochure]. The prohibited medications of strong CYP3A inducer are listed in the Table 6-3 below.

Drugs with a known risk of torsades de pointes (TdP) are prohibited. For identification of drugs with known risk of TdP, please refer to Table 6-4.

Table 6-3 Drugs prohibited while on study

Mechanism of Interaction	Drug Name
Strong CYP3A inducer	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (*Hypericum perforatum*)
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, Jan 2018): drug-drug interactions (DDI) database, 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" This list gets updated periodically. Kindly refer to the above links for latest information.	

Table 6-4 Drugs with a known risk of torsades de pointes prohibited while on study

Class of medication	Drug Name
With known risk of torsades de pointes	amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide,

Class of medication	Drug Name
	procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib
Check: Crediblemeds.org for the most updated list. This list gets updated periodically. Kindly refer to the above links for latest information.	

Additionally, live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, TY21a typhoid vaccines and live COVID-19 vaccines) must not be administered while a participant is on study treatment and for 30 days after the last dose of study treatment. Other types of vaccines with other mechanisms of action such as inactivated vaccines, messenger Ribonucleic Acid (mRNA) vaccines, Deoxyribonucleic Acid (DNA)-based vaccines and viral vector based vaccines are permitted for use.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Subject Number (Subject No.), that is assigned when the participant signs the molecular pre-screening ICF and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is rescreened. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the molecular pre-screening ICF, the participant is assigned to the next sequential Participant No. available.

At the molecular pre-screening visit, the Investigator or designated staff will contact the IRT and provide the requested identifying information for the participant to register him/her into the IRT system. Once assigned, the participant No. must not be reused for any other participant. In case of re-screening a new participant No. will be assigned to participant through the Clinical Data Management System interface and this new participant No. will be provided to IRT for registration as re-screened participant.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study.

Prior to dosing, for all participants who fulfill all inclusion/exclusion criteria, the Investigator or his/her delegate will log on to the IRT system and confirm that the participant fulfills all the inclusion/exclusion criteria by completing the key eligibility criteria checklist embedded in the system. All participants who fulfill all inclusion/exclusion criteria will be assigned to one of the cohorts of interest based on prior treatment status results and information will be collected via IRT:

Cohort 1: Treatment naive participants with *MET* mutations regardless of *MET* gene copy number (GCN)

Cohort 2: Pre-treated participants with *MET* mutations regardless of *MET* GCN

The IRT will also specify medication number of the bottles of capmatinib (INC280) to be dispensed to the participant.

If the participant fails to start treatment for any reason, the reason will be entered into the screening disposition eCRF. IRT must be notified within 2 days if the screened participant failed to start treatment.

6.4 Treatment blinding

This is an open-label study. Treatment will be open to participants, Investigator staff, persons performing the assessments, and the clinical trial team (CTT).

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions, and/or reductions are either recommended or mandated in order to allow participants to continue the study treatment.

The following guidelines should be considered:

Dose reductions are allowed for capmatinib and should follow the dose reduction steps described in Table 6-5 and Table 6-6. For each participant, a maximum of two consecutive dose level reductions is allowed after which the participant must be discontinued. Dose reductions of capmatinib below 200 mg b.i.d. are not permitted. The lowest dose allowed, 200 mg b.i.d. in tablets is expected to be pharmacologically active, as the observed steady state plasma trough concentrations ([CINC280X1101], [CINC280X2202], n=6) were above the concentration associated with full *MET* inhibition in xenograft mice models (IC_{90}, 120 nM total concentration).

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions are permitted in order to allow participants to continue the study treatment. All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the National Cancer Institute (NCI) - CTCAE version 5.0. Any changes must be recorded on the dosage administration eCRF page.

A participant must discontinue treatment with capmatinib if, after treatment is resumed at the lowest allowed dose (200 mg b.i.d.), the toxicity recurs with the same or worse severity despite use of maximal preventive measures as per the institution guidelines for toxicity prevention and management.

Unless otherwise indicated in Table 6-6, for grade 1 and tolerable grade 2 treatment-related toxicities, participants may continue full doses of capmatinib. For intolerable grade 2 or grade 3 treatment-related toxicities, dosing should be interrupted until at least resolution to grade 1 followed by either dose reduction or re-initiation at the same dose level, depending on the type of toxicity as described in Table 6-6. For any grade 4 toxicity, except for neutropenia, febrile neutropenia, anemia and thrombocytopenia, participants should interrupt capmatinib until resolution to grade 1, followed by either dose reduction or treatment discontinuation (refer to Table 6-6).

Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-6 or listed in Section 6.5.2. Deviations to mandatory dose discontinuations are not allowed.

Dose re/escalation of study treatment to previous dose level is allowed only once, and if no AE leading to dose modification is observed after at least 1 cycle (3 weeks) of study treatment at the reduced dose.

Any planned variance from the guidelines in Table 6-6, in view of participant safety (unless there is an urgent need for action) when in the opinion of the Investigator the participant continues to experience clinical benefit, should first be discussed and approved by the Novartis Medical Lead or designee.

Events not included in the study protocol or the reference guidance documents should be managed according to local practices.

Table 6-5 Dose reduction steps for capmatinib

Capmatinib	**Starting dose level 0**	**Dose level - 1**	**Dose level - 2**
	400 mg b.i.d.	300 mg b.i.d.	200 mg b.i.d.
Dose reduction should be based on the worst toxicity demonstrated at the last dose. Dose reduction below 200 mg b.i.d. is not allowed.			

Table 6-6 Criteria for dose reduction / interruption and re-initiation / permanent discontinuation of capmatinib treatment for adverse drug reactions

Worst toxicity CTCAE Grade[a] during a cycle of therapy	
No toxicity	Maintain dose level
HEMATOLOGICAL	
Neutrophil count decreased (ANC) Neutropenia	
Grade 1 (ANC < LLN - 1500/mm3; < LLN - 1.5 x 10^9/L)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm3; < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm3; < 1.0 - 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (ANC < 500/mm3; < 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level
Platelet count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75,000/mm3; < LLN - 75 x 10^9/L)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm3; < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm3; < 50 - 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 < 25,000/mm3; < 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then ↓1 dose level
Febrile neutropenia (ANC < 1000/mm3 (< 1.0 x 10^9/L), fever > 38.3°C)	Omit dose, then: If resolved in ≤ 7 days, resume treatment at ↓ 1 dose level If resolved in > 7 days, permanently discontinue participant from capmatinib treatment
Hemoglobin decreased (Anemia)	
Grade 1 (Hgb <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN – 100 g/L)	Maintain dose level

Grade 2 (Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L)	Maintain dose level
Grade 3 (Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level If toxicity recurs, permanently discontinue participant from capmatinib treatment.
RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at the same dose level.
Grade 3 (> 3.0 - 6.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at ↓ 1 dose level.
Grade 4 (> 6.0 x ULN)	Permanently discontinue participant from capmatinib treatment
HEPATIC	
Isolated Total Bilirubin elevation*	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, ↓1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days, permanently discontinue participant from capmatinib treatment
Grade 4 (> 10.0 x ULN)	Mandatory: Permanently discontinue participant from capmatinib treatment
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3 x ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 if grade 2 elevation at baseline) then If resolved in ≤ 7 days, then resume treatment at the same dose level If resolved in > 7 days, resume treatment at ↓ 1 dose level
Grade 4 (> 20.0 x ULN)	Mandatory: Permanently discontinue participant from capmatinib treatment
Combined elevations of AST or ALT and Total Bilirubin [b,c,d]	
For participants with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis or hemolysis OR For participants with elevated baseline AST or ALT or total bilirubin value:	Mandatory: Permanently discontinue participant from capmatinib treatment

[AST or ALT > 3 x baseline] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN] without evidence of cholestasis or hemolysis	
METABOLIC	
Amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic)	Maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic)	Omit the dose until resolved to ≤ grade 2, then If resolved in ≤ 14 days, resume treatment at the same dose level If resolved in > 14 days, then ↓ 1 dose level
Grade 4 (> 5.0 x ULN with signs or symptoms)	Permanently discontinue participant from capmatinib treatment
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTcF 450-480 ms)	Maintain dose level
Grade 2 (QTcF 481-500 ms)	Maintain dose level
Grade 3 (QTcF ≥ 501 ms on at least two separate ECGs)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
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 participant from capmatinib treatment
GASTROINTESTINAL	
Pancreatitis	
Grade 2	Maintain dose level
Grade ≥ 3	Mandatory: Permanently discontinue participant from capmatinib treatment
Diarrhea**	
Grade 1 (despite appropriate anti-diarrheal medication)	Maintain dose level
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 resume treatment at ↓ 1 dose level
Grade 3 or 4 (despite appropriate anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Vomiting	
Grade 1 (despite appropriate anti-emetics)	Maintain dose level
Grade 2 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then maintain dose level. If vomiting returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level

Nausea	
Grade 1 or 2 (despite appropriate anti-emetics)	Maintain dose level
Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Rash/photosensitivity* **	
Grade 1	Maintain dose level.
Grade 2	Maintain dose level.
Grade 3, despite skin toxicity therapy	Omit dose until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, then resume treatment at ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then permanently discontinue participant from capmatinib treatment
Grade 4, despite skin toxicity therapy	Omit dose and permanently discontinue participant from capmatinib treatment
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Interstitial Lung Disease (ILD) /Pneumonitis	
Monitor participants for pulmonary symptoms indicative of ILD/Pneumonitis. In addition, withhold capmatinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for ILD/Pneumonitis to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage.	
Grade 1	Interrupt capmatinib during diagnostic workup for ILD/Pneumonitis. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib may be restarted at the same dose. If it recurs after resumption of capmatinib, permanently discontinue capmatinib.
Grade 2	Mandatory: Interrupt capmatinib dose during diagnostic workup for ILD until improvement to ≤ Grade 1. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib may be restarted following these guidelines: • If resolves to ≤ Grade 1 in ≤ 7 days reduce capmatinib by 1 dose level • If fails to resolve to ≤ Grade 1 within 7 days or recurs after resumption of capmatinib at decreased dose, permanently discontinue capmatinib
Grade 3 and Grade 4	Mandatory: Permanently discontinue capmatinib Treat with intravenous (i.v.) steroids as clinically indicated. Oxygen therapy as indicated
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	

Fatigue/ Asthenia	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, resume treatment at same dose level If resolved in > 7 days, resume treatment at↓ 1 dose level
Peripheral edema	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue capmatinib treatment
Other adverse events	
Grade 1 or 2	Maintain dose level, consider to initiate appropriate support medication. For any intolerable grade 2 (e.g.: limiting instrumental ADL), consider omitting the dose until resolved to ≤ grade 1, then restart either at same dose or ↓ 1 dose level.
Grade 3	Omit dose until resolved to ≤ grade 1, then↓ 1 dose level
Grade 4	Permanently discontinue participant from capmatinib treatment
LLN: Lower Limit of Normal / ULN: Upper Limit of Normal All dose modifications should be based on the worst preceding toxicity [a] Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0). [b] "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold. [c] "Cholestasis" defined as: ALP elevation (> 2.0 x ULN and R value (ALT/ALP in x ULN) < 2.0) in participants without bone metastasis, or elevation of ALP liver fraction in participants with bone metastasis. [d] If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction. [*] Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the aetiology 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. [**] Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea. [***] During the whole duration of treatment with capmatinib, the participant is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing and avoid sunbathing or using a solarium intensively.	

6.5.2 Treatment interruption and treatment discontinuation

If the administration of capmatinib is temporarily interrupted for reasons other than toxicity up to 21 days, then treatment with capmatinib may be resumed at the same dose. If the treatment with capmatinib is withheld due to toxicity, the dose modification guidelines in Table 6-5 should be followed. In any case, scheduled visits and all assessments (including tumor assessments) should continue to be performed, as described in Table 8-2.

If the treatment with capmatinib is withheld for more than 21 consecutive days (counting from the first day when a dose was interrupted), then study treatment should be permanently discontinued. Under exceptional circumstances, when the Investigator believes that continuing treatment may still derive clinical benefit for the participant, study treatment may be resumed. However, the Investigator must discuss and receive approval from Novartis Medical Lead or designee prior to continuing study treatment and rational should be captured in the source documents.

Participants who discontinue the study due to a study drug related AE or an abnormal laboratory value must be followed as described in Section 6.5.3.

6.5.3 Follow-up for toxicities

All participants will be followed for safety until 30 days after the last dose of capmatinib. Participants 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.

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

Table 6-7 Follow-up evaluations for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION
HEMATOLOGICAL	
Febrile neutropenia, Neutropenia ≥ CTCAE grade 3 Thrombocytopenia ≥ CTCAE grade 3 Anemia ≥ CTCAE grade 3	Test weekly (or more frequently if clinically indicated) until ≤ CTCAE grade 2. Perform physical exam for check on bruising in case of major thrombocytopenia.
RENAL	
Serum creatinine ≥ CTCAE grade 2	Test weekly (or more frequently if clinically indicated) until ≤ CTCAE grade 1 or baseline. Participants will be instructed to increase hydration until resolution to ≤ CTCAE grade 1 or baseline.
HEPATIC	
Isolated total bilirubin elevation	**Total bilirubin CTCAE Grade 1:** Monitor LFTs per protocol or more frequently if clinically indicated **Total bilirubin CTCAE Grade 2:** Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN **Total bilirubin CTCAE Grade 3:** Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. If resolved in > 7 days, after discontinuing the participant from capmatinib permanently, the participant should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks **Total bilirubin CTCAE Grade 4:**

	After discontinuing the participant from capmatinib permanently, the participant should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilization over 4 weeks
Isolated AST/ALT elevation	**AST/ALT CTCAE Grade 2 elevation:** For participants with baseline value ≤ 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN For participants with baseline value > 3.0 – 5.0 x ULN: monitor LFTs per protocol or more frequently if clinically indicated **AST/ALT CTCAE Grade 3 elevation:** For AST/ALT elevation > 5.0 - 10.0 x ULN: For participants with baseline value ≤ 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN For participants with baseline value > 3.0 – 5.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs, weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN For AST/ALT elevation > 10.0 - 20.0 x ULN: Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ baseline **AST/ALT CTCAE Grade 4 elevation:** Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
Combined elevations in ALT and/or AST with concurrent total bilirubin increase, in the absence of cholestasis or hemolysis	Combined elevations of AST or ALT and total bilirubin: After discontinuing the participant from capmatinib permanently, repeat LFTs as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Core LFTs consist of ALT, AST, Gamma-Glutamyl Transferase (GGT), total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)
METABOLIC	
Amylase or lipase ≥ CTCAE grade 3	Test weekly (or more frequently) until ≤ CTCAE grade 2. A Computerized Tomography (CT) scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥ CTCAE grade 3 result, to exclude disease progression or potential other liver or pancreatic disease.
CARDIAC	
≥ CTCAE grade 3	Test weekly (or more frequently) until ≤ CTCAE grade 2.

QTcF ≥ 501 ms (CTCAE grade 3)	When QTcF ≥ 501 ms (CTCAE grade 3), perform the following: Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Review concomitant medication usage for the potential to prolong the QT-interval. Check compliance with correct dose and administration of capmatinib. Perform a repeat ECG within one hour of the first QTcF of ≥501 ms. If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once daily until the QTcF returns to < 501 ms. Repeat ECGs 7 days and 14 days (and then every 21 days) after dose resumption for all participants who had therapy interrupted due to QTcF ≥ 501 ms. If QTcF of ≥ 501 ms recurs, repeat ECGs as described above. Notes: The Investigator should contact the Novartis Medical Lead or designee regarding any questions that arise if a participant with QTcF prolongation should be maintained on study.
GASTROINTESTINAL	
Diarrhea	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 participant should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practice and the Investigator's best judgment and may follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004). For example: For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at a standard dose (e.g. initial administration of 4 mg, then 2 mg every 2-4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures should be considered. Note: complicating signs or symptoms include: moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration. For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms), management should involve intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg sub-cutaneous tid or 25 to 50 µg IV) and antibiotics (e.g. fluoroquinolone) should be given.
Nausea and Vomiting	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 participants with vomiting, the participant 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.
SKIN TOXICITY	
Rash and Photosensitivity	
CTCAE grade 1	Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
CTCAE grade 2	Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids).
≥ CTCAE grade 3	Intensify appropriate skin toxicity therapy and monitor weekly or more frequently until resolved to grade ≤ 2
Peripheral edema	
CTCAE grade≤2	Consider to initiate conservative measures such as leg elevation, compression stockings, and dietary salt modification as clinically indicated.
CTCAE grade≥3	Initiate/intensify conservative measures
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
ILD/Pneumonitis	
CTCAE Grade 1	CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression- re-image at least every 3 weeks Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection Monitoring of oxygenation via pulse oximetry recommended Consultation of pulmonologist recommended
CTCAE Grade 2	CT scan (high-resolution with lung windows) • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Pulmonary function tests [a] - if normal at baseline, repeat every 8 weeks • Bronchoscopy with biopsy and/or BAL recommended [c] Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated) [b]
CTCAE Grade 3 and Grade 4	CT scan (high-resolution with lung windows) Clinical evaluation and laboratory work-up for infection Consult pulmonologist Pulmonary function tests[a]-if < normal, repeat every 8 weeks until ≥ normal Bronchoscopy with biopsy and/or BAL if possible[c] Treat with i.v steroids (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours)[b]. If i.v. steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication

[a] PFT (Pulmonary function tests) to include: diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for hemoglobin; spirometry; resting oxygen saturation.

Guideline for significant deterioration in lung function: Decrease in spirometry and/or DLCO of 30% and/or O2 saturation ≤ 88% at rest on room air.

[b] Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. Consider tapering dosage at end.

[c] If bronchoscopy is performed, bronchoalveolar lavage (BAL) should be done where possible to exclude alveolar hemorrhage, opportunistic infections, cell count + determination lymphocyte CD4/8 count where possible.

6.5.3.1 Follow-up on potential drug-induced liver injury cases

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe drug-induced liver injury (DILI) and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

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

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT >3.0 x baseline] OR [ALT or AST > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed to be the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/ International Normalized Ratio (INR), alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is also recommended.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – e.g. using computerized tomography (CT), magnetic resonance imaging (MRI), or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, Endoscopic Retrograde Cholangio-Pancreatography (ERCP) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants 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 whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. In clinical

situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-8 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-8 Specific assessments to rule out possible causes of LFT abnormalities

Disease	Assessment
Hepatitis A (HAV), Hepatitis B (HBV), Hepatitis C (HCV), Hepatitis E (HEV)	Immunoglobulin M (IgM) anti-HAV; Hepatitis B virus surface Antigen (HBsAg), IgM & Immunoglobulin G (IgG) anti-Hepatitis B core antibody (anti-HBc), HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
Cytomegalovirus (CMV) Herpes Simplex Virus (HSV) Epstein-Barr Virus (EBV) infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, Immunoglobulin E (IgE), Immunoglobulin A (IgA)
Alcoholic hepatitis	Ethanol history, GGT, mean corpuscular volume (MCV), CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic congestive heart failure, hypotension, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Ceruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, thyroid stimulating hormone (TSH); cardio vascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes mellitus/ glycogenic hepatitis).

Obtain PK sample to determine exposure to study treatment and metabolites.

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as a serious adverse event (SAE).

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," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Each time the study treatment is to be administered, IRT needs to be accessed for the medication (kit) number. The date of all study drug administered during the study and any deviations from the protocol treatment schedule will be captured by the Investigator staff or by field monitor on the appropriate study treatment dispensing form.

The Investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed.

Compliance will be assessed by the Investigator and/or study personnel at each visit using pill counts and information provided by the participant. This information should be captured in the source documents at each visit. All study drug dispensed and returned must be recorded in a drug accountability log. Compliance to the protocol will be assessed by the field monitor at each visit and the information provided by the pharmacist or by the Investigator. Exposure to the study treatment will be based on the amount of drug administered.

Pharmacokinetic parameters will be determined in all participants treated with capmatinib, as detailed in pharmacokinetics section (Section 8.6.2).

6.6.2 Emergency breaking of assigned treatment code

Not applicable. Study is open-label.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational drug section (Section 6.1.1).

The Investigator or responsible site personnel must instruct the participant (or caregiver) to take the study treatment as per protocol. Study treatment will be dispensed to the participant by authorized site personnel only. All dosages prescribed to the participant and all dose changes during the study must be recorded on the study treatment eCRF.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

As per Section 4.6, during a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster) that limits or prevents on-site study visits, delivery of Investigational Medicinal Product (IMP) directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate

or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 30-day supply. In this case, regular phone calls or virtual contacts (every 3 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.7.1 Handling of study treatment and other treatment

6.7.1.1 Handling of study treatment

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

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

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

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment. The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, at the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.7.1.2 Handling of other treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

The Investigator or responsible site personnel must instruct the participant or caregiver to take the study treatment as per protocol.

Capmatinib tablets will be administered orally on a continuous b.i.d. dosing schedule from Day 1 to Day 21 of each 21 day cycle. The starting dose of capmatinib will be 400 mg b.i.d. (total daily dose = 800 mg) on a flat scale of mg/day and not individually adjusted by weight or body surface area.

A complete cycle of treatment is defined as 21 days of twice daily treatment with capmatinib.

- Including days of PK sampling, participants should take 400 mg of capmatinib tablets b.i.d. at approximately the same time each day starting at Cycle 1 Day 1.
- Each dose of capmatinib is to be taken with a glass of water (at least 8 ounces - approximately 250 mL) and consumed over as short a time as possible (i.e., not slower than 1 tablet every 2 minutes).
- Participants should be instructed to swallow the tablets whole and not to chew them.
- Capmatinib can be administered with or without food. The morning and the evening dose should be taken 12 (± 4) hours apart, although a 12-hour interval is highly recommended. The morning dose should be taken at the same time each morning. If a dose is not take within 4 hours of the planned dosing time, the missed dose should not be replaced.
- On days when PK blood samples are to be collected, participants will be instructed to hold their dose until arrival at the study center, unless participant visit is more than 4 hours post standard visit time. Capmatinib will be administered at the site in the morning prior to the post-dose PK sample blood draws supervised by a member of the research team. The pre-dose PK samples will be taken right before capmatinib administration. The exact time of drug administration should be recorded in the appropriate eCRF. Food consumption prior to capmatinib administration should be recorded in the appropriate eCRF. If a participant vomits within 4 hours of capmatinib dosing, the time of vomiting should be recorded on the eCRF.
- Participants should be instructed not to make up for missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined when the full dose is not taken within 4 hours of the scheduled twice daily dosing. If that occurs, then the dose (or part of the remaining dose) should not be taken and dosing should restart with the next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose.
- During the whole duration of treatment with capmatinib, the participant is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, avoid sunbathing or using a solarium).

7 Informed consent procedures

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative (defined as per local regulation) and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulation (CFR) 50, local regulations, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, privacy and data protection requirements, where applicable, and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative (defined as per local regulation).

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional research, which include the use of samples for *in vitro* diagnostic test (e.g. companion diagnostic [CDx]) development. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

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

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Information about common side effects already known about the investigational treatment can be found in the [capmatinib Investigator's Brochure]. This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational treatment that is identified between Investigator's Brochure (IB) updates will be communicated as appropriate, for example, via an Investigator Notification (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Molecular pre-screening informed consent
- Main study informed consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- Patient information sheet for female partners of any male participants who took study treatment

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.6, during a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster) that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The assessment schedule (Table 8-2) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Written informed consent must be obtained before any study specific assessments are performed. Main screening evaluations and baseline radiological tumor assessments should be performed within 28 days of treatment start. All visits are to be scheduled according to the appropriate number of calendar days from Cycle 1 Day 1 of study drug administration. Visit windows per Table 8-1 are allowed.

Table 8-1 Allowable window for participant assessments

Visit name	Window allowed
Screening	28 days to -1 day from first dose of study treatment
C1D1	Within 3 days after confirmation of eligibility in IRT system
C1D15	± 1 day
C2D1	± 3 days
C3D1	± 3 days
Day 1 visit of all subsequent cycles	± 3 days
Imaging evaluations	± 7 days
PROs assessments	± 7 days
EOT	≤ 7 days after stopping study treatment
30-Day Safety FUP	+ 7 days
Survival FUP	± 14 days

Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol. If a given visit is out of window, the next visit should be performed with reference to the day of first dose in order to get the participant back on schedule. If an off-schedule imaging assessment is performed, subsequent imaging assessments should be performed in accordance with the original imaging schedule. Missed or rescheduled visits should not lead to automatic discontinuation.

The “X” in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The “S” in the table denotes the assessments that are only in the participant’s source documentation and do not need to be recorded in the clinical database.

PRO measure(s) must be completed before any clinical assessments are performed at any given visit.

As per Section 4.6, during a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster) that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls or virtual contacts (e.g. tele consultation) or visits by site staff/off-site healthcare professional(s) staff to the participant’s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 8-2 Assessment schedule

Period	**Screening**		**Treatment**						**Post-Treatment FUP**			**Survival FUP**
Visit Name	**Molecular Pre-Screening**	**Screening**	**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PRO FUP**	**End of Post-Treatment FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 1**	-	-	-	-	-
Molecular pre-screening informed consent	X											
Collection of EGFR and ALK status	X											
Information on prior local testing for *MET*Δex14 mutation status	X											
Archival tumor or newly obtained tumor biopsy (preferred) sample for central confirmation of *MET*Δex14 mutation status (via a validated test) and to support CDx development	X											
IRT pre-screening registration	X											
Main informed consent		X										

Period	**Screening**		**Treatment**						**Post-Treatment FUP**			**Survival FUP**
Visit Name	**Molecular Pre-Screening**	**Screening**	**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PRO FUP**	**End of Post-Treatment FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 1**	-	-	-	-	-
Demography	X											
IRT eligibility check		S										
IRT registration		X	X		X	X	X	X				
Inclusion / Exclusion criteria	X	X										
Medical history/current medical conditions		X										
Diagnosis and stage of cancer	X											
Smoking history		X										
Prior antineoplastic therapy (meds, surgery, radiation)		X										
Prior/concomitant medications		Continuously from 28 days prior to first dose until 30 days after last dose of study treatment								X[1,2]		
Physical examination, including neurological exams		S	If clinically indicated									
Targeted physical examination			S		S	S	S	S				
Performance status (ECOG)		X	X		X	X	X	X		X[1]		

Period	**Screening**		**Treatment**						**Post-Treatment FUP**			**Survival FUP**
Visit Name	**Molecular Pre-Screening**	**Screening**	**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PRO FUP**	**End of Post-Treatment FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 1**	-	-	-	-	-
Body Height		X										
Body Weight		X	X		X	X	X	X				
Vital Signs		X	X	X	X	X	X	X				
HIV history		S										
Hematology		X	X	X	X	X	X	X				
Chemistry		X	X	X	X	X	X	X				
Coagulation		X	If clinically indicated									
Urinalysis with microanalysis		X	If clinically indicated									
Pregnancy Test (serum)		S						S				
Pregnancy test (urine)			S		S	S	S					
CT scan or MRI of chest, abdomen		X				C3D1 and then every 6 weeks		EOT scan not required if previous scan was performed ≤ 28 days		Every 6 weeks		
Pelvis CT or MRI		X				C3D1 and every 6 weeks (if positive at baseline) or if clinically indicated		If positive at baseline or if clinically indicated. EOT scan not required if previous scan was performed within ≤28 days		Every 6 weeks (if positive at baseline) or if clinically indicated		
Brain MRI (Brain CT is acceptable if		X				C3D1 and every 6 weeks (if positive at		If positive at baseline or if clinically indicated. EOT scan		Every 6 weeks (if positive at		

Period	**Screening**		**Treatment**						**Post-Treatment FUP**			**Survival FUP**
Visit Name	**Molecular Pre-Screening**	**Screening**	**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PRO FUP**	**End of Post-Treatment FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 1**	-	-	-	-	-
MRI contrast is contraindicated)						baseline) or if clinically indicated		not required if previous scan was performed within ≤28 days		baseline) or if clinically indicated		
Whole body bone scan		X				If clinically indicated				If clinically indicated		
Localized bone CT, MRI or x-ray (for any lesions identified on the whole body bone scan that are not visible on chest/ abdomen or pelvis (CAP) CT or MRI)		Only if lesions on whole body scan that are not visible on the CAP scans				C3D1 and every 6 weeks (if positive at baseline) or if clinically indicated		If positive at baseline or if clinically indicated. EOT scan not required if previous scan was performed within ≤28 days		Every 6 weeks (if positive at baseline) or if clinically indicated		
CT or MRI of other metastatic sites (e.g. neck)		Only if other metastatic sites suspected				C3D1 and every 6 weeks (if positive at baseline) or if clinically indicated		If positive at baseline or if clinically indicated. EOT scan not required if previous scan was performed within ≤28 days		Every 6 weeks (if positive at baseline) or if clinically indicated		
Color photography (for skin lesions)		Only if skin lesions				C3D1 and every 6 weeks (if positive at baseline) or if clinically indicated		If positive at baseline or if clinically indicated. EOT scan not required if previous scan was performed within ≤28 days		Every 6 weeks (if positive at baseline) or if clinically indicated		

Period	**Screening**		**Treatment**						**Post-Treatment FUP**			**Survival FUP**
Visit Name	**Molecular Pre-Screening**	**Screening**	**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PRO FUP**	**End of Post-Treatment FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 1**	-	-	-	-	-
Adverse Events		Continuously from signing of main ICF until 30 days after last dose of study treatment										
Serious Adverse Events	Continuously from signing of pre-screening ICF until 30 days after last dose of study treatment. Before signing of screening ICF, only SAEs suspected to be causally related to a study procedure are captured								SAEs related to study treatment only			
Electrocardiogram (ECG)		X	X[3]		X[3,4]			X				
PROs (EORTC QLQ-C30, EORTC LC13, EQ-5D-5L and NCCN Fact-FBrSI)			X			Starting at Cycle 3 and then every 6 weeks		X		Every 6 weeks		
Capmatinib administration			Continuous twice daily dosing [b.i.d.]									
Plasma collection for assessment of *MET*Δex14 status and development of a liquid CDx			X[3]									
Food administration					X							
Blood for capmatinib PK					X[3,5]	X[3]						
Antineoplastic therapies (meds, surgery, radiation) since discontinuation of study drug								X	X	X	X	X

Period	**Screening**		**Treatment**						**Post-Treatment FUP**			**Survival FUP**
Visit Name	**Molecular Pre-Screening**	**Screening**	**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PRO FUP**	**End of Post-Treatment FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 1**	**Day 1**	-	-	-	-	-
Disposition		X						X			X	
Survival (survival information can be obtained via telephone contact)												X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Only for participants with brain metastasis at baseline
[2] Only for steroids
[3] Pre-dose
[4] Post-dose, 2 hours
[5] Post-dose, 0.5-1.5 hour, 3-5 hours

8.1 Molecular pre-screening

In order to be considered eligible for the study, participants must have *MET*Δex14 mutation confirmed by a Novartis-designated central laboratory. If a participant's *MET* mutation status is known via a local result, confirmation by a Novartis-designated central laboratory is required to confirm eligibility prior to starting study treatment but participant can commence screening. Confirmation by the Novartis-designated central laboratory will be by a RT-PCR (a real time Reverse Transcription (RT) Polymerase Chain reaction (PCR) test that detects exon 14-deleted *MET* messenger Ribonucleic Acid (RNA) derived from formalin fixed, paraffin-embedded human tissue) to confirm eligibility prior to starting study treatment but participant can commence screening.

All participants will be asked to sign and date an IRB/IEC approved "Molecular pre-screening informed consent form" before their tumor sample is sent for testing to the Novartis-designated central laboratory. Freshly cut slides from a newly obtained tumor biopsy (preferred) or archival tumor tissue should be submitted to the Novartis designated laboratory to test for *MET*Δex14 mutation status. The resulting *MET*Δex14 data and remaining tumor tissue material (upon the approval from health authorities) may be used in the development of an *in vitro* diagnostic test for *MET*Δex14, such as a CDx.

Archival tumor tissue obtained at the time of diagnosis of NSCLC or any time since is acceptable. If more than one archival tissue sample is available, tissue from the most recent biopsy is preferred. Samples obtained from bone metastases and cytology samples are not acceptable. All tissue samples need to have >20% tumor content per slide.

- If resection sample, 5 slides are requested per participant initially and if sufficient tumor material is not found to perform the *MET*Δex14 mutation analysis, additional slides (not exceeding a total of 10 slides overall) will be requested.
- If core needle biopsy, 10 slides are requested per participant.

If a newly obtained biopsy is provided, the remaining tissue from pre-screen failure samples will be returned to the site.

The pre-screening results from central testing for all tested participants (whether the participant is eligible or not for the study) will be communicated to the respective study center.

If confirmed that the participant's tumor harbors the required mutation, the participant will be able to proceed for study specific screening procedures following signature of the main ICF.

8.2 Screening

The study IRB/IEC approved informed consent form must be signed and dated before any screening procedures are performed, except for laboratory and radiological evaluations which were performed as part of the participant's clinical standard of care within the acceptable screening window.

Participants will be evaluated against study inclusion and exclusion criteria and safety assessments (refer to Table 8-2). Screening assessments must be repeated if performed outside of the specified screening window (Table 8-1). Participants must meet all inclusion and none of the exclusion criteria at screening in order to be eligible for the study.

Laboratory assessments of hematology/chemistry performed as part of the screening evaluations done within 7 days prior to Cycle 1 Day 1 will not be required to be repeated in Cycle 1 Day 1, unless deemed clinically necessary by the Investigator. Serum pregnancy test is preferentially within 72 hours prior to treatment start. Urine pregnancy test on Cycle 1 Day 1 will not be required if serum pregnancy test is done within 72 hours prior to Cycle 1 Day 1.

Laboratory test result(s) or symptoms that do not satisfy the eligibility criteria may be repeated or treated during the screening visit window. In the event that the repeated laboratory test(s) cannot be performed within 28 days from the original screening visit, or do not meet the eligibility criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screening failure.

Re-screening of a participant who has failed screening may be allowed. In such cases, a new ICF must be signed. A new participant number will be assigned to the participant. The re-screen form will have to be completed in the eCRF and in IRT to provide the original participant number.

All required screening assessments must be repeated if they do not meet the allowed time window for screening when the participant is re-screened for participation in the study. An individual participant can only be re-screened once for the study.

Once the number of participants enrolled is likely to ensure target number of treated participants, the Sponsor may close the study to further screening. In this case, the participants who screen failed will not be permitted to re-screen.

Participants who are screened and eligibility confirmed in IRT system, but fail to start treatment for any reason, the reason should be recorded on the appropriate disposition eCRF.

8.2.1 Eligibility screening

Following registering in the IRT for screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.2.2 Information to be collected on screening failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not entered in the study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Participants who sign the molecular pre-screening ICF, or the molecular pre-screening and main ICFs and are subsequently found to be ineligible will be considered as screen failures and data will be handled in the same manner.

The reason for screen failure should be recorded on the appropriate disposition eCRF (screening phase disposition).

The following eCRF pages must be completed for screening failure patients:

- *ALK* and *EGFR* status as per participant's record
- Information on prior local testing for *MET* mutation status (if available)
- Tumor samples collection (archival or newly obtained) for central confirmation of *MET* mutation status
- NSCLC diagnosis and extent of disease, including:
  - Date of diagnosis and stage of NSCLC
  - Site of active disease
  - Characteristics of disease
- Screening phase disposition
- Demography
- Informed consent
- Inclusion/Exclusion Criteria
- Withdrawal of consent (if applicable)
- Death (if applicable)

No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the screening period (see SAE section for reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure (i.e. tumor biopsy collection) will be reported to the Novartis Safety group. Data and samples collected from participants prior to screen failure may still be analyzed, unless the participant withdraws the consent of using the data and samples by writing (or having the legal representative /guardian written) to the Investigators.

Participants who sign an informed consent form and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.3 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data that need to be collected on all participants at screening include:

- Demography (age, gender)
- Other background or relevant medical history (including smoking history) / (serious) adverse events
- Cancer characteristics including diagnosis, history, extent of cancer, baseline tumor mutation status (*EGFR*, *ALK* and *MET*), prior antineoplastic therapies (medications, radiation, surgeries), and for participants eligible for cohort 2, the date of progression prior to study entry
- Tumor imaging assessments
- Other assessments to be completed for the purpose of determining eligibility (ECOG performance status, complete physical examination, vital signs, hematology, chemistry, coagulation studies, urinalysis, HIV testing [only recorded in source documentation], serum pregnancy test for women of child-bearing potential [only recorded in source documentation], and 12-Lead ECG)

- Prior and current concomitant medications and surgical and medical procedures

Data to be collected on C1D1 pre-dose include:

- Patient Reported Outcomes (PROs)
- 12-Lead ECG

8.4 Efficacy assessments

Planned time points for all efficacy assessments are provided in Section 8 Visit schedule and assessments.

8.4.1 Tumor imaging assessments

Tumor response will be assessed locally and centrally according to the Novartis guideline version 3.2 (Section 16.1) based on RECIST 1.1 (Eisenhauer et al 2009). In addition, CNS lesions will be assessed centrally according to the Novartis guideline version 1 based on Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria (Section 16.2).

The imaging assessment collection plan is presented in Table 8-3. Details of the central review process will be described in the independent review charter.

Participants should have at least one documented measurable lesion at study entry per RECIST 1.1.

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The results of the central evaluations will be used for primary analysis purposes. The local Investigator's assessment will be used for the secondary endpoint analysis and treatment decision making.

Although the study will use an Independent Central Radiology Review to measure tumor response, the decision to enroll the participant will be made based on the judgment of the Investigator and local radiologist.

Information regarding prior interventions (e.g. radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening and prior interventions should be transmitted to the imaging CRO via the Baseline Clinical Form along with the baseline images for review by the independent radiologist. Once the participant is enrolled, the baseline imaging data should be sent within 2 business days by the study site to the Independent Central Radiology Reviewer for imaging assessments. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

Information regarding cytology results should be transmitted to the imaging CRO via the Cytology Form for all visits, when applicable, for review by the independent radiologist. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

Information regarding ECOG performance status and corticosteroid dose as compared to baseline should be transmitted to the imaging CRO for review by a neuro-radiologist.

Details regarding collection and shipment of additional information required for imaging assessment including RANO-BM assessment by BIRC will be described in the imaging manual provided by the designated CRO.

As per Section 4.6, during a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster) that limits or prevents on-site study visits, the collection of images (e.g. change of imaging center or imaging frequency) may be modified by Novartis and will be communicated to the Investigator.

Table 8-3 Imaging assessment collection plan

Procedure	Screening/Baseline*	During Treatment/Follow-up
Chest and abdomen CT or MRI (with intravenous contrast enhancement)	Mandated	Mandated **Starting at Cycle 3:** every 6 weeks (+/- 7 days) thereafter until PD determined using RECIST 1.1 by the Investigator and confirmed by BIRC **End of treatment:** scan not required if previous scan was done within 28 days **Post Treatment Follow-Up:** for participants with EOT for reason other than disease progression, withdrawal of consent or death will continue collect imaging and follow the same rule of every 6 weeks (+/- 7 days) thereafter until PD.
Pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Only if lesions were documented at screening; follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated
Brain MRI with intravenous contrast enhancement	Mandated	Only if lesions were documented at screening; follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated.
Whole body bone scan	Mandated	If clinically indicated
Localized bone CT, MRI or x-ray	Mandated for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	Only if lesions were documented at screening; follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated.
Color photography (with scale/ruler)	Mandated for any skin lesions present	Only if lesions were documented at screening; follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated
CT or MRI of other metastatic sites (e.g. neck)	If other metastatic sites are suspected	Only if lesions were documented at screening; follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated
*Preferably 7 days prior to first dose, however, scans within 28 days of first dose are acceptable		

8.4.1.1 Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (preferably Day -7 to Day -1 prior to Cycle 1 Day 1).

Any imaging assessments already completed during the regular work-up of the participant 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 treatment cannot be considered baseline images. The following assessments are required at screening:

- Chest, abdomen, and pelvis CT or MRI
- Brain MRI
- Whole body bone scan
- Localized bone CT, MRI, or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen, and pelvis CT or MRI
- Color photography for any skin lesions present
- CT or MRI of other metastatic sites (e.g. neck), if clinically indicated

If a participant is known to have a contraindication to CT intravenous 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 should be performed.

Regardless of the suspicion of brain metastases at baseline, contrast enhanced brain MRI must be completed for all participants unless MRI contrast is contraindicated. If MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

A whole body bone scan should be performed per institutional standard of care [e.g. Tc-99m bone scan, whole body bone MRI, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), or 18F-sodium fluoride (NaF) positron emission tomography (PET)]. Localized CT, MRI, or x-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen or pelvis CT/MRI.

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

If skin lesions are present at screening, color photography should be acquired using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph.

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

Chest x-rays and ultrasound should not be used to measure tumor lesions.

8.4.1.2 Post-baseline imaging assessments

Imaging assessments as described in Table 8-3 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing see (Table 8-2). Imaging assessments for response evaluation will be performed started at Cycle 3 every 6 weeks (+/- 7 days) thereafter until disease progression, death, lost to follow-up or withdrawal of consent/opposition to use data. Imaging assessments should be scheduled using the date of first dose of study treatment as the reference date (not the date of the previous tumor assessment) and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed. If an unscheduled imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Additional imaging assessments may be performed at any time during the study at the Investigator's discretion to support the efficacy evaluations for a participant, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging 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.

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 i.v. contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease (PD) per RECIST 1.1 (Section 16.1).

All study imaging (including any off-schedule imaging studies) should be submitted to the designated imaging CRO for quality control and central review.

8.4.1.3 Confirmation of disease progression by BIRC

Time points at which progression is determined locally

All participants who have disease progression determined by the local Investigator require an expedited central review. Rapid image transmission to the imaging CRO may be accomplished by transferring the images electronically, e.g. via the Internet. In all instances, the process at the imaging CRO will ensure that the central reviewers remain blinded to the results of the local assessment and the expedited nature of the review. The Investigator seeking an expedited review to confirm the disease progression seen locally must indicate this request to the imaging CRO on a designated form or by alternative means. The imaging will undergo expedited central review (within 5 business days from the time of image receipt at the imaging CRO and once all applicable queries are resolved**)** and the results of the central review will be communicated to the site. While the Investigator is awaiting the results of the central review, it is preferable that the participant continue on study treatment. However, during this time, the Investigator should do whatever is medically necessary for his/her participant.

If the central review determines disease progression, then the participant will discontinue study treatment and subsequent tumor assessments are no longer required.

If the central review does not determine disease progression, the participant should continue receiving the study treatment until disease progression has been determined by the BIRC or, as a minimum requirement, until at least one additional tumor assessment has been completed, unless there is a medical need (i.e. rapid progression or clinical deterioration) for an immediate change in therapy.

Participants will continue to have imaging performed as per protocol (Table 8-2) until the central review determines disease progression.

The imaging vendor will ensure that the central reviewers involved are blinded to the expedited status of the reading.

Time points without locally determined progression

All imaging time points without locally determined progression will be read on an ongoing, non-expedited basis as detailed in the imaging manual to be provided by the designated imaging CRO and independent review charter. Results of these readings will not be communicated to the sites.

Treatment beyond disease progression

Following determination of disease progression, if the Investigator believes the participant may derive benefit from continuing study treatment, the participant will be permitted to continue treatment beyond initial disease progression as per RECIST 1.1. Please see Section 6.1.5.1 for additional information.

8.4.1.4 Efficacy follow-up imaging assessments

For participants who discontinue treatment for reasons other than initial disease progression as per RECIST 1.1, tumor assessments must continue to be performed as outlined in Table 8-2. Please refer to Section 9.3.2 for additional information.

8.4.2 Appropriateness of efficacy assessments

Tumor assessments every 6 weeks are consistent with the standard clinical practice. Chinese Society of Clinical Oncology (CSCO) guidelines for NSCLC recommend response assessment every 6-12 weeks and respect assessment frequency defined in clinical trials by drug evaluation needs.

Conducting tumor evaluations more than this frequency may expose a participant to an unnecessary treatment if disease progression takes place between infrequent assessments.

8.4.3 Overall survival

All participants will enter the survival follow-up period once they complete the safety follow-up and efficacy follow-up after treatment discontinuation (whichever is longer). Survival status will be collected every 12 weeks regardless of treatment discontinuation reason (except if consent is withdrawn or participant is lost to follow-up) until death, lost to follow-up, or withdrawal of consent for survival follow-up.

Additional survival assessments may be performed outside the 12 weeks follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.

Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs. Information on the therapies received for NSCLC, if any, after study treatment has been completed will be collected, as well as the SAEs suspected to be related to study treatment.

8.5 Safety

Safety will be monitored by assessing physical examination, Eastern Cooperative Oncology Group (ECOG) Performance Status, vital signs, body weight, ECG, Patient reported outcomes (PRO), laboratory assessments including hematology, chemistry, coagulation and urinalysis, as well as collecting AEs at every visit. Clinically relevant findings that were present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant new findings that begin or worsen after informed consent which meet the definition of an AE must be recorded as an AE. For details on AE collection and reporting, refer to AE Section 10.1.1.

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

As per Section 4.6, during a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster) that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 3 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-4 Assessments & specifications

Assessment	Specification
Physical examination	Significant findings that were present prior to the signing of informed consent must be included as medical history on the participant's eCRF. Significant new findings that begin or worsen after informed consent must be recorded as an AE on the appropriate eCRF. **Physical examination** At screening, a complete physical examination will be performed and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a basic nervous system evaluation. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated. Information about the physical examination must be present in the source documentation. **Targeted physical examination** A targeted physical exam will be performed at day 1 of each cycle during treatment and at EOT as indicated in Table 8-2, except where a complete physical examination is required (see above). It will include at least the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). If indicated based on symptoms, additional exams will be performed. Information for all physical examinations must be included in the source documentation at the study site and additionally reported in appropriate eCRF pages for blood pressure (SBP and DBP), vital signs, height and weight. For

Assessment	Specification
	participants with brain metastasis neurological status will also be evaluated at the time of radiological assessments.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature. They will be measured at screening and at subsequent time points as specified in Table 8-2.
Height and weight	Height in centimeters (cm) will be measured at screening. Body weight in kilogram (kg) (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-2.
Performance status	The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale as specified in Table 8-5 and following the schedule given in Table 8-2.

The Eastern Cooperative Oncology Group (ECOG) performance status scale will be used as described in Table 8-5 following the schedule given in Table 8-2.

Table 8-5 ECOG performance status

Grade	ECOG 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 house work, 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

8.5.1 Laboratory evaluations

Local laboratories will be used for the analysis of all scheduled and unscheduled hematology, chemistry, coagulation, urinalysis with microanalysis, and pregnancy test to assess the participant's eligibility and safety monitoring (as detailed in Table 8-2 and Table 8-6). Additional time points should be added as deemed necessary as per the Investigators best judgment to make sure dose adjustments are performed to safeguard the safety of the participant. Additional results from unscheduled laboratory evaluations should be recorded in the appropriate Unscheduled Visit eCRF.

Laboratory assessments of hematology/chemistry performed as part of the screening evaluations done within 7 days prior to Cycle 1 Day 1 will not be required to be repeated on Cycle 1 Day 1, unless deemed clinically necessary by the Investigator. Serum pregnancy test is preferentially within 72 hours prior to treatment start. Urine pregnancy test on Cycle 1 Day 1 will not be required if serum pregnancy test is done within 72 hours prior to Cycle 1 Day 1. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Table 8-1) except as stated above.

If at any time a participant has a laboratory parameter obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory. The results of all local laboratory results will be recorded in the appropriate eCRF. The Investigator is responsible for reviewing all laboratory reports for participants and evaluating any abnormalities for clinical significance.

As per Section 4.6, during a public health emergency as declared by local or regional authorities' (i.e. pandemic, epidemic or natural disaster), that limits or prevents on-site study visits, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

Table 8-6 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands (optional, if clinically indicated), Other)
Chemistry	Albumin, Alkaline phosphatase, ALT, Amylase, AST, Creatinine, Creatinine Clearance, Total Bilirubin, Direct Bilirubin (only if total bilirubin is ≥ grade 2), Gamma-glutamyl-transferase (GGT), Lipase, Calcium, Magnesium, Sodium, Potassium, Phosphate (inorganic phosphorus), fasting Glucose (non-fasting allowed post-baseline), Blood Urea Nitrogen (BUN) or Urea Bicarbonate or arterial blood gas analysis (i.e. partial pressure of oxygen in blood (pO2), partial pressure of carbon dioxide in blood (pCO2) and pH): (optional, if clinically indicated) Chloride and Uric Acid: at screening and thereafter optional, if clinically indicated.
Urinalysis	Microscopic panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	International normalized ratio (INR) and Prothrombin time (PT), or Quick Test (QT)
Pregnancy Test	A serum pregnancy test must be performed at screening before C1D1 (preferentially ≤72 hours before C1D1) and at EOT. A urine pregnancy test should be performed at Day 1 of every cycle. For women considered to be post-menopausal and not of child-bearing potential, pregnancy testing is not required. If a serum pregnancy test is required as per local practice at day 1 of every cycle, the urine pregnancy test does not need to be repeated.

8.5.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline/according to the ECG Investigator manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

Standard 12 lead ECG will be performed as per Table 8-7.

The individual ECGs should be recorded approximately 2 minutes apart. The Fridericia QT correction formula (QTcF) should be used for clinical decisions. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each participant.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or AEs as appropriate.

ECGs are to be collected with machines available at the site. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate eCRF. Each ECG tracing should be labeled with the study number, participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate eCRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as AEs.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the Investigator.

Table 8-7 Local ECG collection plan

Cycle	Day	Time	ECG Type
Screening	Day -28 to Day -1	Anytime	12 Lead, triplicate
Cycle 1	Day 1	Pre-dose	12 Lead, triplicate
Cycle 2	Day 1	Pre-dose	12 Lead, triplicate
Cycle 2	Day 1	Post-dose 2 hours	12 Lead, triplicate
End of Treatment		Anytime	12 Lead, triplicate
Unscheduled		Anytime if clinically indicated	12 Lead, triplicate

8.5.3 Pregnancy and assessments of fertility

Participants are required to use highly effective methods of contraception during the study and for the follow-up time period as specified in Section 5.2. For a definition of highly effective contraception, assessment of fertility (males and females), and the definition of post-menopausal, please refer to Section 5.2.

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test preferentially within 72 hours prior to the first dose of study treatment and at the end of treatment.

Urine pregnancy tests will be required to be performed on Day 1 of every cycle.

In case of a positive urine pregnancy result, **the participant must contact** the Investigator immediately and the study treatment must be stopped until additional tests are performed to confirm pregnancy (including a confirmatory serum pregnancy test).

Male participants must notify the Investigator in case their partner becomes pregnant during the treatment period. See Section 10.1.4 for pregnancy reporting.

As per Section 4.6, during a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster) that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g. following country specific measures).

Assessments of Fertility

A woman is considered of childbearing potential from menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation, confirming permanent sterilization, or if the post-menopausal is not clear, the Investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.5.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.6 Additional assessments

8.6.1 Patient reported outcomes (PRO)

A PRO is a measurement based on a report that comes from the study participant about the status of a participant's health condition without interpretation of the participant's report by anyone else. A PRO can be measured by self-report or by interview, provided that a trained interviewer records only the participant's response. Symptoms or other unobservable concepts known only to the participant (e.g. pain severity or nausea) can only be captured by PRO measures. PROs can also assess the participant's perspective on functioning or activities that may also be observable by others.

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30, and QLQ-LC13), the EuroQoL 5-level instrument (EQ-5D-5L, tablet version) and the NCCN FACT-Brain Symptom Index version 2.0 (NCCN-FACT-FBrSI) will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms, treatment-related adverse experiences, and global health status. The EORTC QLQ-C30 and QLQ-LC13 are frequently used in clinical trials of participants with advanced or metastatic lung cancer (Aaronson et al 1993).

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients which has been translated and validated into 81 languages and has been used in more than 3,000 studies worldwide. The questionnaire contains 30 items and is composed of both multi-item scales and single-item measures based on the patients experience over the past week. These include five scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/Quality of Life (QoL) scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of

symptomatology/problems. All scoring will follow the scoring procedures defined by the EORTC Scoring Manual (Fayers 2001).

The QLQ-LC13 is used in conjunction with the EORTC QLQ-C30 and provides information on an additional 13 items specifically related to lung cancer. The five domains of the LC13 include pain, dyspnea, coughing and hemotoposis, and are based on their presence over the past week. All but the pain domain are scored on a 4 point Likert scale ranging from "not at all" to "very much". Pain is score based on its presence, hence yes or no. A higher score indicates a higher presence of symptoms (Bergman et al 1994).

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (The EuroQol Group 1990). The EQ-5D 5L is designed for self-completion by respondents and takes only a few minutes to complete. Instructions to respondents are included in the questionnaire. The EQ-5D-5L consists of 2 pages – the descriptive system and the EuroQoL visual analogue scale (EQ VAS) (Herdman et al 2011). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The participant is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The EQ VAS records the participant's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine' (Rabin and de Charro 2001).

The NCCN FACT-Brain Symptom Index version 2.0 (NCCN-Fact-FBrSI) symptom module will be used to explore changes in symptoms associated with potential brain metastases in this study. The NCCN FACT-FBrSI was adapted from the previously developed FACT-Brain module. The symptoms module contains 24 items with a recall period of the past 7 days. The participant responds to 24 statements and indicates to what extent it applies to them on a 5-point Likert response scale from "not at all" to "very much." (Lai et al 2014).

PRO data collection will be collected using an electronic device. All PRO assessments should be administered in the participant's local language and according to the Visit Evaluation Schedule in Table 8-2, prior to any tests, treatments or receipt of results from any test to avoid biasing the participant's perspective. The PRO questionnaires should be completed at Cycle 1 Day 1, Cycle 3 Day 1 and then every 6 weeks while the participant is on treatment, at the end of treatment visit, and at the post-treatment follow-up visits if the participant is still followed for efficacy. All PRO questionnaires will also be accessible during unscheduled visits and can be completed at Investigator/site team discretion.

Participants should be given sufficient space and time to complete all study questionnaires, and all administered questionnaires should be reviewed for completeness. If missing responses are noted, participants should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all participants, including from those who discontinue prior to the end of treatment or follow-up visit, however, if participants refuse to complete questionnaires, this should be documented in study source records. A participant's

refusal to complete study questionnaires is not a protocol deviation. The participant should be made aware that completed measure(s) are not reviewed by the Investigator/ study personnel.

8.6.2 Pharmacokinetics

Blood samples for PK evaluation will be collected from all treated participants participating in the study. CCI

Complete dosing information, including the date and time of actual blood draw and time of the last study drug dose prior to the sampling, should be obtained on all sampling days and recorded on the PK eCRF and/or CRO requisition form(s).

If vomiting occurs within 4 hours following capmatinib administration on the day of post dose PK blood sampling, PK sample collection is at site's discretion. If PK sample collection is done, the clock time of vomiting should be recorded in the dosage administration PK eCRF page.

8.6.2.1 Pharmacokinetic blood collection and handling

PK blood samples for capmatinib will be collected for all the participants as outlined in Table 8-8.

Table 8-8 Pharmacokinetic blood collection log

Cycle	Day	Scheduled Time Point	Dose Identity (ID) following trough PK sampling	Dose ID prior to trough PK sampling	PK Sample No
2	1	Pre-dose[1]	1	10[2]	101
2	1	Anytime within 0.5-1.5 hour post-dose	1		102
2	1	Anytime within 3-5 hours post-dose	1		103
3	1	Pre-dose[1]	2	20[2]	104
Unscheduled		Anytime[3]			1001+[3]

[1] Take samples immediately prior to administration of capmatinib.
[2] Dose reference IDs with two digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample.
[3] Sample numbers for any unscheduled blood collection for capmatinib will be labeled sequentially starting with 1001.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. A total of 3 mL of blood will be collected at specified time points for capmatinib analysis in plasma. Refer to the study's laboratory manual for detailed instructions for the collection, handling, and shipment of PK samples.

If participants experience a SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained whenever possible. The date and time of the last dose and the time of PK blood draw should be recorded.

8.6.2.2 Analytical method

Pharmacokinetic samples for capmatinib will be quantified using validated liquid chromatography tandem-mass spectrometry (LC/MS/MS) assays.

8.6.3 Biomarkers

Biomarker assessments in tumor

Archival or newly acquired core or excisional biopsy (preferred) are required as part of the molecular pre-screening portion of this trial to test for *MET*Δex14 mutation. Residual tumor sample material (upon the approval of health authorities) and resulting *MET*Δex14 test data may be used to support development of an *in vitro* diagnostic test for *MET*Δ ex14, such as a CDx test. No tissue will be collected in this study for exploratory analyses.

Biomarker assessments in blood

Blood samples will be collected at Cycle 1 Day 1 to assess the association of *MET*Δex14mutation status in ctDNA isolated from blood plasma with capmatinib (INC280) efficacy, how well the *MET*Δex14 status can be detected in blood as compared to tumor tissue and potentially also for development of a liquid biopsy *in vitro* diagnostic test for *MET*Δex14, such as a CDx test.

Biomarker sample collection information should be recorded on the appropriate eCRF and/or Central Laboratory paper requisition form(s). The details must be specified in the protocol.

Table 8-9 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
Tumor samples			
Mandatory for eligibility Formalin fixed paraffin embedded (FFPE) tissue slides from either a newly obtained biopsy (preferred) or from an archival biopsy taken at time of NSCLC diagnosis or any time since; to determine *MET*Δex14 status for eligibility and to support CDx development	5-10 fresh-cut slides (with minimum of 20% tumor content per slide). • If resection sample, 5 slides requested initially and if there is not sufficient tumor material found to perform the MET exon 14 mutation analysis, additional slides (not exceeding a total of 10 slides overall) will be requested. • If core needle biopsy, 10 slides requested.	Pre-Screening Requires participant's written consent on the Molecular Pre-screening ICF	Prior to main screening
Blood samples			
Mandatory Blood (for plasma extraction) for *MET*Δex14 analysis and to support CDx development	2x10 mL	Cycle 1 Day 1	Pre-dose

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation from study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration, if any) and can be initiated by either the participant or the Investigator.

The Investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Investigator decision
- Pregnancy (see Section 10.1.4)
- Any situation in which continued study participation might result in a safety risk to the participant
- Disease progression per RECIST 1.1 as determined by Investigator and confirmed by BIRC. In some circumstances participants may be allowed to continue to receive study treatment beyond disease progression as per RECIST 1.1. These participants will continue assessments as outlined in Table 8-2 or Table 8-3, as applicable, and will complete the EOT visit only after permanent discontinuation of study treatment
- AE requiring permanent discontinuation of study treatment (see Section 6.5.1)
- Protocol deviation that results in a significant risk to participant's safety
- Withdraw of consent (see Section 9.2)
- Study is terminated by the sponsor (see Section 9.4)
- Death
- Lost to follow-up (see Section 9.1.3)

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (Table 8-2).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

The Investigator must also contact the IRT to register the participant’s discontinuation from study treatment.

In some circumstances participants may be allowed to continue to receive study treatment beyond disease progression as per RECIST 1.1 criteria. These participants will continue

assessments as outlined in the assessments section, and will complete the EOT visit only after permanent discontinuation of study treatment.

9.1.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.2 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in the assessment table (refer to Section 8).

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Study completion and post-study treatment

For individual participant: Study completion is reached when participant completes all post-treatment follow-up (including 30-day safety follow-up and tumor assessment until PD, whichever is longer). The appropriate disposition eCRF must be completed, giving the date and reason of post-treatment follow-up discontinuation. After this, participant can enter survival follow-up.

For the study: Study completion is defined as the earliest occurrence of one of the following:

- All participants have discontinued study treatment and completed the safety follow-up and at least 75% of the participants have died, withdrawn consent or are lost to follow-up.
- Another clinical study becomes available that can continue to provide capmatinib in this participant population, and all participants ongoing are transferred to that clinical study. Note: For participants who transfer to another clinical study or an alternative treatment option to continue provision of study treatment, the follow-up for safety, disease progression and survival will not be performed.
- If the primary analysis of ORR or secondary analysis of PFS does not demonstrate treatment benefit, the follow-up for OS will end, in this case the end of the study will be when all participants have discontinued treatment and completed the safety follow-up, or have withdrawn consent or are lost to follow-up.

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to participants who in the opinion of the Investigator are still deriving clinical benefit.

Details on the timing of the primary analysis and final reporting of data are provided in Section 12.

9.3.1 Follow-up for safety evaluations

Regardless of the reason for discontinuation from study treatment (see Section 9.1.1), participants will be contacted for a safety follow-up 30 days (+ 7 days) after the last dose of capmatinib. At this time, the Investigator will record any AEs/SAEs that may have occurred after discontinuation of study treatment and/or follow on resolution of ongoing AEs.

If the participant begins any post-treatment antineoplastic medication before the 30-day safety follow-up period is complete, the collection of new SAEs and AEs unrelated to capmatinib will stop, and, thereafter, only suspected AEs and suspected SAEs will continue to be collected up to day 30. Suspected SAEs will continue to be collected beyond the 30-day safety follow-up.

AEs, concomitant medications and antineoplastic therapies since discontinuation of study treatment will be recorded on the appropriate eCRF during this follow-up period.

For participants who transfer to another Novartis clinical study or Novartis treatment setting, the 30-day safety follow-up will no longer be performed within the present protocol.

9.3.2 Efficacy follow-up and PROs

All participants who discontinue treatment with capmatinib for any reason other than disease progression according to RECIST 1.1 as determined by Investigator and confirmed by BIRC, death, withdrawal of consent for further assessments or lost to follow-up will continue to have tumor assessments as per their current schedule until disease progression is confirmed by BIRC, death, withdrawal of consent for further assessments, lost to follow-up or study terminated by the sponsor. Participants will also continue to complete PRO questionnaires following the same schedule as that for tumor assessments (as per Table 8-2).

When a participant discontinued from efficacy follow-up, the appropriate disposition eCRF must be completed, giving the date and reason of discontinuation, as per Table 8-2.

Information on new antineoplastic therapy initiated since discontinuation of study treatment will be collected on the appropriate eCRF during this follow-up period.

9.3.3 Survival follow-up

Participants will enter the survival follow-up period once they complete the 30-day safety follow-up and efficacy follow-up (if applicable) after treatment discontinuation (whichever is longer). Participants will then be contacted by telephone every 12 weeks to follow-up on their survival status. Any new antineoplastic therapies that have been started since the last contact date will also be collected during these phone calls.

Every effort should be made to comply with the survival follow-up schedule and ensure collection of participant survival data.

9.4 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to):

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study treatment development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. 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 participant's interests. The Investigator or Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found respectively in Section 10.1.1 and Section 10.1.2.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.1.3.

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participant and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

For participants whose *MET* mutation status is unknown and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 10.1.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured as AEs.

Participants whose *MET* mutation status is known will sign the main study ICF.

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. AEs also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade (version 5.0).

AEs will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, life-threatening and fatal, corresponding to grades 1 - 5, will be used. CTCAE grade 5 (death) will be used in this study and information about deaths will be collected through a Death eCRF.

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All AEs must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/permanently discontinued

6. Its outcome

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 AEs only, if improvement to a lower grade is determined, a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

AE monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an AE is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to 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 SAE, except if the Investigator considers that progression of malignancy is related to study treatment.

AEs separate from the progression of malignancy (for 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 treatment.

Information about adverse drug reactions for the investigational drug can be found in the [capmatinib Investigator's Brochure].

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any AE [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - 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 participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that

do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered SAE irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. If a new antineoplastic therapy is initiated during the 30-day safety follow-up period, only SAEs suspected to be related to the study treatment will be collected in the Adverse Events eCRF.

- Screen Failures (e.g. a participant who is screened but is not treated): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.
- Treated Participants: Only SAEs suspected to be causally related to a study procedure are captured between the time participant signs molecular pre-screening ICF and signs the main ICF. All SAEs are collected between the time the participant signs the main ICF until 30 days after the participant has permanently stopped study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the [capmatinib Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an IN to inform all Investigators involved in any study with the same study treatment 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 European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in China.

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

Any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 7 days after capmatinib treatment has been stopped.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with an AE/SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional safety monitoring

Not applicable.

10.3 Committees

10.3.1 Steering committee

A steering committee (SC) will be established comprising Investigators participating in the trial and/or key opinion leaders in NSCLC and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

11 Data collection and database management

11.1 Data collection

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 Electronic Data Capture (EDC) system until they have been trained.

Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

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

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 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 World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, screen failures and study completion, as well as data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original

informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in monitoring guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH Good Clinical Practice (GCP), and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

12 Data analysis and statistical methods

Primary safety and efficacy analysis will be conducted on all participant data by cohort when all treated participants in that cohort have completed at least 6 cycles of treatment (18 weeks) unless a participant has discontinued treatment earlier. These data will be summarized in the primary Clinical Study Report (CSR). In case of one cohort finishes earlier than the other, the primary CSR may be written based on data from that cohort only. Once the second cohort is complete another CSR may be written.

All available data from all participants up to this cutoff date will be analyzed.

12.1 Analysis sets

12.1.1 Full analysis set (FAS)

The full analysis set (FAS) comprises all participants to whom study treatment has been assigned and who received at least one dose of capmatinib. Unless otherwise specified, all efficacy analyses will be performed using FAS.

12.1.2 Full analysis set – brain metastases (FAS-BM)

The full analysis set - brain metastases (FAS-BM) comprises all participants in the FAS who have measurable and/or non-measurable brain metastases at baseline.

12.1.3 Safety set

The Safety Set includes all participants who received at least one dose of capmatinib. Unless otherwise specified, all safety data will be analyzed by Safety Set.

12.1.4 Pharmacokinetics analysis set

The pharmacokinetic analysis set (PAS) consists of all participants who received at least one dose of capmatinib and had at least one evaluable post-baseline capmatinib concentration measurement.

The definition of an evaluable PK concentration will be specified in the statistical analysis plan (SAP).

12.1.5 Evaluable set

The evaluable set comprises all participants in FAS who have at least one post-baseline tumor assessment after treatment.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by cohort 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. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by cohort using FAS.

12.3 Treatments

The safety set will be used for the analyses below.

The actual dose and duration in days of capmatinib as well as the dose intensity (computed as the ratio of total dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized by cohort. Dose reductions and dose interruptions (including the reasons for these) will be listed and summarized by cohort.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) by cohort.

12.4 Analysis supporting primary objectives

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the ORR by cohort as per BIRC review. ORR is defined as the proportion of participants with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will be performed on the FAS. The primary efficacy endpoint ORR will be estimated and the exact 95% confidence interval (CI) (Clopper and Pearson 1934) will be provided by cohort.

The study is based on estimation of the endpoint and therefore no statistical hypothesis will be performed.

12.4.3 Handling of intercurrent events of primary estimand

Tumor assessment data collected irrespective of treatment discontinuation until the start of new anti-cancer therapy will be included to derive BOR.

If any antineoplastic therapy is taken, any response after the antineoplastic therapy will be considered as non-responder. In case of any missed visit in the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), the subsequent assessments will be included for the BOR calculation.

12.4.4 Handling of missing values/censoring/discontinuation

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

Participants with a BOR of 'Unknown' per RECIST 1.1 will be considered as non-responders when estimating ORR and DCR.

Participants who have disease progression and continue to receive study drug after progression will qualify for PD at the time of progression and will be counted as PD in the derivation of efficacy endpoints. For additional details, please ref to RECIST 1.1 guideline (Section 16).

12.4.5 Sensitivity analyses

Sensitivity analysis will be performed for DOR and PFS. In the sensitivity analysis of DOR and PFS, for participants who receive antineoplastic therapy, the event will be censored at the last tumor assessment prior to the antineoplastic therapy.

12.4.6 Supplementary analysis

No supplementary analysis will be provided.

12.4.7 Supportive analyses

ORR by BIRC will be summarized by evaluable sets to support the primary analysis.

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or pharmacodynamic endpoint(s)

Duration of response (DOR)

DOR only applies to participants whose BOR is complete response (CR) or partial response (PR) according to RECIST 1.1 based on tumor response data. The start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to any cause. DOR will be assessed as per BIRC review and by Investigator assessment for both FAS and evaluable sets.

Participants continuing without progression or death due to any cause will be censored at the date of their last adequate tumor assessment. Participants without a post-baseline tumor assessment will be censored at the time of the first treatment.

ORR by Investigator assessment

The evaluation of ORR will be also conducted based on Investigator assessment. ORR will be estimated and the exact binomial 95% CI will be provided by cohort.

Time to Response (TTR)

TTR is defined as the time from the date of start of study drug to the first documented response of either complete response (CR) or partial response (PR), which must be subsequently confirmed (although date of initial response is used, not date of confirmation). TTR will be evaluated as per BIRC and also by Investigator review and according to RECIST 1.1.

Participants without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e. first patient first visit (FPFV) to last patient last visit (LPLV)) for participants with a PFS event (i.e. disease progression or death due to any cause), or at the date of the last adequate tumor assessment for participants without a PFS event.

Disease control rate (DCR)

DCR is defined as the proportion of participants with a BOR of complete response (CR), or partial response (PR), or an overall response of stable disease (SD). DCR will be assessed as per BIRC as well as Investigator assessment according to RECIST 1.1.

DCR and its 95% exact confidence interval will be presented for each cohort using FAS.

Progression-free survival (PFS)

The analysis in this section refers to the PFS as per BIRC and per Investigator review.

PFS is defined as the time from the date of first dose of capmatinib to the date of the first documented progression according to RECIST 1.1, or death due to any cause. If a participant has no progression or death, the participant is censored at the date of last adequate tumor assessment. Definition of last adequate tumor assessment is provided in Section 16.1.

PFS will be summarized using the Kaplan-Meier (KM) method, based on data from the FAS. Median PFS, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for PFS proportions at specific timepoints, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

Overall survival (OS)

OS is defined as the time from date of first treatment to date of death due to any cause. If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date).

All time to event (TTE) variables (DOR, TTR, PFS, OS) distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, and 95% confidence intervals of the medians (in months) along with 25th and 75th percentile will be presented for each cohort using FAS.

Overall intracranial response rate (OIRR)

OIRR is calculated based on response assessments in the brain for participants having measurable and/or non-measurable brain metastases at baseline. OIRR is the proportion of participants with a confirmed best overall intracranial response (BOIR) of CR or PR per RANO-BM criteria as assessed by BIRC review.

OIRR calculated based on the data from the FAS-BM and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented by cohort.

Intracranial disease control rate (IDCR)

IDCR is calculated based on response assessments in the brain for participants having measurable and/or non-measurable brain metastases at baseline. IDCR is the proportion of participants with a confirmed BOIR of CR or PR or SD (or non-CR/non-PD) per RANO-BM criteria as assessed by BIRC review.

IDCR calculated based on the data from the FAS-BM and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented by cohort.

Time to intracranial response (TTIR)

TTIR is defined as the time from the date of the start of study treatment to the date of the first documented intracranial response of either CR or PR per RANO-BM criteria as assessed by the BIRC review, which must be subsequently confirmed (date of initial response is used, not date of confirmation).

All participants in the FAS-BM will be included in TTIR calculations. Participants without a confirmed intracranial CR or PR will be censored at the study-maximum follow-up time (i.e. LPLV−FPFV) for participants with an intracranial PFS event (intracranial progression or death due to any cause), or at the date of the last adequate tumor assessment in brain for participants without an event.

Median TTIR with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. TTIR will be summarized using the KM method, based on data from the FAS-BM. KM estimates for TTIR proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

Duration of intracranial response (DOIR)

DOIR only applies to participants whose confirmed BOIR is CR or PR per RANO-BM criteria as assessed by the BIRC review. DOIR is defined as the time from the date of first documented intracranial response of either CR or PR to the date of the first documented intracranial progression per RANO-BM criteria as assessed by BIRC review or date of death due to any cause.

Participants with a confirmed intracranial CR or PR will be censored if they have disease progression in organs other than brain and have no scans in brain after that. The censoring date will be the date of the last adequate tumor assessment in brain.

DOIR will be summarized using the KM method. Median DOIR, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for DOIR proportions at specific timepoints, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

12.5.2 Safety endpoints

12.5.2.1 Analysis set and grouping for the analysis

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

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

1. Pre-treatment period: from day of participant'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.

12.5.2.2 Adverse events

All information obtained on AEs will be displayed by cohort and participants.

The number (and percentage) of participants with treatment emergent AEs (events started on or after the first dose of study medication) will be summarized in the following ways:

- by primary system organ class and preferred term.
- by primary system organ class, preferred term and maximum severity.
- by Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant AEs leading to discontinuation.

A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

AEs which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study treatment relationship, or developed into SAEs after the start of the treatment period.

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs.

SAEs, non-serious AEs and adverse events of special interest (AESI) based on case retrieval strategy (CRS) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths, and SAEs (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.

12.5.2.3 Vital signs

All vital signs data will be listed by cohort, participant, and visit and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by cohort and visit/time.

12.5.2.4 12-lead ECG

ECG evaluation will be collected as per visit schedule (see Table 8-2).

- PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally.

All ECG data will be listed by cohort, participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by cohort and visit/time.

12.5.2.5 Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or higher. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests by cohort:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition to the above mentioned tables and listings, other exploratory analyses, CCI [redacted]

12.5.2.6 Other safety evaluations

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

12.5.3 Pharmacokinetics

The PAS will be used in all pharmacokinetic data analysis and PK summary statistics.

Descriptive summary statistics of plasma concentration will be provided by cohort and by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), Standard Deviation, CV% (arithmetic and geometric), median, minimum and maximum.

Capmatinib plasma concentration data will be listed by cohort, participant, and visit/sampling time point.

Capmatinib plasma concentration values below the lower limit of quantitation (LLOQ) will be displayed in listings as zero with a flag and handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and their CV.

If data permits, population PK analysis CCI [redacted].

12.5.4 DNA

Not applicable.

12.5.5 Biomarkers

As a project standard, only biomarker data collected in the clinical database will be analyzed. This study is not adequately powered to assess specific biomarker related hypotheses. The analyses of biomarkers will be reported in the CSR if data are available at the time of clinical database lock and CSR preparation. Otherwise, the results may be reported in a separate report document.

There may be circumstances when a decision is made to stop a sample collection, or not perform or discontinue the analysis of tumor samples due to either practical or strategic reasons (e.g., issues related to the quality and or quantity of samples. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed.

12.5.5.1 Outline of the data analysis

The proposed data analysis will be aligned with the secondary biomarker objective of the protocol:

- To evaluate the association between *MET* mutation status as measured in ctDNA at baseline with ORR, DOR and PFS upon treatment with capmatinib.

12.5.5.2 Data handling principles

Data handling principles such as handling of missing values, categorization of continuous or semi-continuous biomarker, etc. will be described in detail in the SAP.

12.5.5.3 Data analysis principles

12.5.5.3.1 Analysis set

The FAS will be used for all biomarker analyses. Unless otherwise specified, all statistical analyses of biomarker data will be performed on participants with biomarker data.

12.5.5.3.2 Basic tables, figures and listings

If the number of participants is considered large enough, the association between *MET* mutation status as measured in ctDNA at baseline with ORR, DOR and PFS will be established using Kaplan-Meier curve, by cohort separately. Median survival together will their 95% confidence intervals will be reported. 95% CI will be generated for ORR using Fisher exact test.

Details of statistical methods will be provided in the SAP.

12.5.5.3.3 Advanced analysis methods

CCI [redacted]

12.5.6 Pharmarcokinetics/Pharmacodynamics relationships

Not applicable.

12.5.7 Patient reported outcomes

Patient reported outcomes (PRO) data will be analyzed using the FAS.

The EORTC QLQ-C30/LC13, NCCN FACT-Br Symptom Index symptom module and EQ-5D-5L questionnaires will be used to collect participant's PRO data. Scoring and handling of missing data from PROs will be conducted according to the respective scoring manual provided by the developers (Fayers 2001; Van Reenen M et al 2019).

Descriptive statistics for continuous data will be used to summarize EORTC QLQ-C30/LC13, EQ-5D-5L, and NCCN FACT-FBrSI at each scheduled assessment time point. The scores will be displayed as mean profiles by cohort/sub-cohort, presented over time. The number of

participants completing the questionnaires and the number of missing or incomplete assessments will be summarized for each scheduled assessment time point.

12.6 Analysis of exploratory endpoints

Not applicable.

12.7 Interim analyses

Not applicable.

12.8 Sample size determination

12.8.1 Primary endpoint(s)

Approximate 35 participants will be treated in this two-cohort study (cohort 1 ~ 15 participants and cohort 2~20 participants). With 15 participants in Cohort 1, the lower bound of exact binomial 95% CI for observed ORR will be at least 38.4% when observed ORR is 66.7%. Similarly, with 20 participants in Cohort 2, the lower bound of exact binomial 95% CI for ORR will be ≥ 19.1% when observed ORR is 40%.

Table 12-1 below shows the results from study [CINC280A2201] which will be used as a reference for sample size calculation.

Table 12-1 Objective response rate (ORR) and 95% lower limit of confidence interval (LLCI) (%) in study CINC280A2201

Line	n/N	Point estimate (%)	95% LLCI (%)
1L	19/28	67.9	47.6
2/3L	28/69	40.6	28.9

In study [CINC280A2201], 67.9% ORR and 47.6% of its lower limit of 95% CI were observed from 28 participants in the treatment naive cohort. If 10 responders out of 15 participants are observed in this study, cohort 1, it will result ORR of 66.7%. The probability of observing ORR greater than 47.6% is at least 0.89. With 15 participants, Table 12-2 below shows the probability of observing ORR greater than 47.6%.

Table 12-2 Operating characteristics for cohort 1

Sample size	True ORR (%) in Chinese participants	Probability (%) that observed ORR > 47.6% (lower limit in A2201)
15	50	50.0
	55	65.4
	60	78.7
	65	88.7
	70	95.0
	75	98.3

Similarly, in study [CINC280A2201], 40.6% ORR and 28.9% of its lower limit of 95% CI were observed from 69 participants from the pre-treated cohort. If 8 responders out of 20 participants are observed in this study, cohort 2, it will result 40% ORR. The probability of observing ORR

greater than 28.9% is at least 0.87. With 20 participants, Table 12-3 below shows the probability of observing ORR greater than 28.9%.

Table 12-3 Operating characteristics for cohort 2

Sample size	True ORR (%) in Chinese participants	Probability (%) that observed ORR > 28.9% (lower limit in A2201)
20	25	38.3
	30	58.4
	35	75.5
	40	87.4
	45	94.5
	50	99.4

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Signing 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 Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

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

13.2 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

13.3 Quality control and quality assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of Investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures (SOPs), and are performed according to written Novartis processes.

13.4 Participant Engagement

Not applicable.

13.5 Data Protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an 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 and health authorities, where required, it cannot be implemented.

14.1 Protocol amendments

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 prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant 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.

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16 Appendices

16.1 Appendix 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 3.2: 16-Feb-2016 Version 3.1: 29-Nov-2011 Version 3: 19-Oct-2009 Version 2: 18-Jan-2007 Version 1: 13-Dec-2002
Release date:	11-Feb-2016
Authors (Version 3.2):	PPD
Authors (Version 3.1):	PPD
Authors (Version 3):	PPD
Authors (Version 2):	PPD
Authors (Version 1):	PPD

Glossary

BOR	Best overall response
CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
DOR	Duration of response
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

16.1.1 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 16.1.2 and the definition of best response in Section 16.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.1.3.2 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 16.1.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.1.2 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.

16.1.2.1 Definitions

16.1.2.1.1 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 16.1.3.2.8

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 10 mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5 mm 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 [redacted] 15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring [redacted] 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.

- 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.

16.1.2.1.2 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 16.1.3.2.8.

16.1.2.2 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.
- 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 major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. 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 new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
  - 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.
  - Physical exams: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10 mm size, and can be assessed using calipers.
  - Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. 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, lactate dehydrogenase (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 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 (SD). Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and SD (an effusion may be a side effect of the treatment) or progressive disease (PD) (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.

16.1.2.3 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 16.1.2.1.1.
- **Nodal target**: See Section 16.1.2.1.1.

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.

16.1.2.4 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 for the target (Table 16-1) and non-target lesions (Table 16-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-3) as well as the presence or absence of new lesions.

16.1.2.4.1 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.

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.

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.

16.1.2.4.2 Determination of target lesion response

Table 16-1 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] In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.1.2.2).

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 possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as PD
- 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 16-1 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 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.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert

judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.1.2.4.3 Determination of non-target lesion response

Table 16-2 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[2]

1. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail.
2. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- 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 there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- 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 16.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.1.2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- 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 16.1.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of PD 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 16.1.2.2.

16.1.2.5 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 16-3.

Table 16-3 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

Target lesions	Non-target lesions	New Lesions	Overall lesion response

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 16.1.2.4.

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

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.

16.1.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.1.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.1.3.1 Best overall response

The best overall response (BOR) 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 BOR 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 BOR 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 BOR derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the BOR 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 BOR for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

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

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

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 BOR.

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 BOR 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 BOR will be based on the sequence of central blinded review/calculated (central) overall lesion responses.

Based on the patients' BOR during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a BOR 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 BOR of CR or PR or SD. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a BOR of CR or PR, or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

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 PD 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 BOR 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).

16.1.3.2 Time to event variables

16.1.3.2.1 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, PFS is censored at the date of last adequate tumor assessment.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

16.1.3.2.2 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.

16.1.3.2.3 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.

16.1.3.2.4 PFS2

A recent EMA guidance (EMA 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this

document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues w.r.t. censoring foreseen.

16.1.3.2.5 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.

16.1.3.2.6 Duration of response (DOR)

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 DOR 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 DOR 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.

16.1.3.2.7 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 ORRs, since the same kind of selection bias may be introduced as described for DOR in Section 16.1.3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

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

16.1.3.2.8 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.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

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

For the calculation of DOR 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 PD.
- 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 16.1.3.2.8).

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

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment

date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.

- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

16.1.3.2.9 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 non-measurable disease is derived slightly differently according to Table 16-4.

Table 16-4 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 16.1.2.4.

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 BOR patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

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

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

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

16.1.3.2.10 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 16.1.3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 16-5 Options for event dates used in PFS, TTP, DOR

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) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and DOR)

1. =Definitions can be found in Section 16.1.3.2.7.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.1.3.2.7.
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.

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) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DOR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DOR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

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 16-5 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.

16.1.4 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).

16.1.4.1 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).

16.1.4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

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

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems

- Participant/guardian decision
- 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)

Death is a reason which "*must*" lead to discontinuation of patient from trial.

16.1.4.3 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
- Participant/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.1.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment 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). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) 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.

16.1.4.5 Programming rules

The following should be used for programming of efficacy results:

16.1.4.5.1 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.

16.1.4.5.2 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 16.1.3.2.7). 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.

16.1.4.5.3 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.

16.1.4.5.4 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)'.

16.1.4.5.5 Study/project specific programming

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

16.1.4.5.6 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 DORs) 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 16-5)
- Death due to reason other than underlying cancer *(only used for TTP and DOR)*
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 16.1.3.2.7. 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.

16.1.5 References (available upon request)

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16.2 Appendix 2: Guidelines for Response Assessment in Neuro-oncology (RANO) for Brain Metastases (BM)

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List of abbreviations

BM	Brain metastases
BOIR	Best overall intracranial response
CNS	Central Nervous System
CR	Complete response
DCR	Disease Control Rate
DOIR	Duration of Intracranial Response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FPFV	First Patient First Visit
IDCR	Intracranial Disease Control Rate
KM	Kaplan-Meier
LD	Longest diameter
LPLV	Last Patient Last Visit
MRI	Magnetic resonance imaging
NCRNPD	Non-CR/Non-PD
NE	Not evaluable
OIRR	Overall Intracranial Response Rate
PD	Progressive disease
PR	Partial response
RANO	Response Assessment in Neuro-Oncology
RANO-BM	Response Assessment in Neuro-Oncology brain metastases criteria
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
TTIR	Time to Intracranial Response

16.2.1 Introduction

This guideline provides the general principles and application of the Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM) criteria to assess tumor response and to derive efficacy endpoints in Novartis oncology brain metastases trials. This guideline is based on the publication: "Response assessment criteria for brain metastases: proposal from the RANO group" (Lin 2015).

In studies with an endpoint of overall intracranial response rate (OIRR), tumor response will be primarily evaluated by the Response Assessment in Neuro-Oncology (RANO) working group Brain Metastases criteria, the RANO-BM Criteria (Lin 2015).

The standard response and progression criteria from RANO-BM are relevant for the assessment of parenchymal brain metastases only. Leptomeningeal metastases, which are generally not radiographically measurable in a reliable and reproducible manner, will be treated as for non-target lesions.

Similar to RECIST 1.1 (Eisenhauer et al 2009), definitions for radiographical response in RANO-BM are based on unidimensional measurements. Participants will undergo gadolinium-enhanced MRI* assessments for response evaluation as defined in the protocol.

The efficacy assessments described in Section 16.2.2 and the definition of best overall intracranial response in Section 16.2.3.1 are based on the RANO-BM criteria but also give more detailed instructions and rules for determination of best response. Section 16.2.3.2 is summarizing the endpoints and related variables.

The following components will be taken into account when assessing a participant's overall intracranial response at an individual evaluation:

- Tumor evaluation for gadolinium-enhanced MRI assessments
- Overall lesion response category (CR/PR/PD/SD (or non-CR/non-PD)/NE)
- Corticosteroid usage
- ECOG performance scale and other clinical evaluation findings

*In this document, the term "MRI" refers to gadolinium-enhanced MRI.

16.2.2 Efficacy assessments

Tumor evaluations are made based on RANO-BM (Lin 2015).

Tumor assessments will be performed according to assessment schedule described in the protocol Section 8.

16.2.2.1 Definitions

16.2.2.1.1 Disease measurability

In order to evaluate CNS tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline.

Measurable disease

Measurable disease is defined as a contrast-enhancing lesion that can be accurately measured in at least one dimension, with a minimum size of 10 mm, and is visible on two or more axial slices that are preferably 5 mm or less apart with 0 mm skip (and ideally ≥1.5 mm apart with 0 mm skip). Additionally, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable. If the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least double the slice thickness. Interslice gaps, if present, should also be considered in the determination of the minimum size of measurable lesions at baseline.

Non-measurable disease

Non-measurable disease includes all other lesions, including:

- Other measurable lesions that cannot be considered as target lesions
- lesions with longest dimension less than 10 mm,
- lesions with borders that cannot be reproducibly measured,
- dural, bony skull metastases,
- cystic-only lesions, and
- leptomeningeal disease.

Lesions composed of a tumor around a cyst or a surgical cavity are considered non-measurable unless there is a nodular component that measures 10 mm or more in longest diameter and 5 mm or more in perpendicular plane. The cystic or surgical cavity should not be measured for the determination of a response. Non-measurable lesions should all be followed as non-target lesions.

16.2.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the participant may be allowed to enter the study in some situations (e.g. studies including participants with leptomeningeal disease). Guidance on how participants with just non-measurable disease at baseline will be evaluated for response is given in Section 16.2.3.4.

16.2.2.2 Methods of tumor measurement – general guidelines

Participants will undergo gadolinium-enhanced MRI assessments for response evaluation as defined per protocol.

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

- All measurements should be taken and recorded in metric notation (mm) using a digital measurement tool.
- All baseline evaluations should be performed as closely as possible to randomization/start of treatment and never more than 28 days before the randomization/start of treatment.
- The same method of assessment and technique (gadolinium- enhanced MRI) should be used to characterize each identified and reported lesion at baseline and during follow-up.

16.2.2.2.1 Special Circumstances

In the case of participants who have been treated with stereotactic radiosurgery or immunotherapy-based approaches, for whom there has been radiographical evidence of enlargement of target and non-target lesions, which do not necessarily represent tumor progression, if radiographical evidence of progression exists, but clinical evidence indicates that the radiological changes are due to treatment effect (and not due to progression of cancer), additional evidence is needed to distinguish between true progression and treatment effect. In this case, standard MRI alone is insufficient. Participants can continue on protocol therapy pending further investigation with one or more of the following options:

- The MRI can be repeated at the next protocol-scheduled assessment or sooner, and generally within 6-8 weeks. The investigator can choose a shorter time interval if progressive symptoms or other clinical concerns arise.
  - Continued tumor growth might be consistent with radiographical progression, in which case the participant should discontinue the study.
  - Stabilisation and shrinkage of a lesion can be consistent with treatment effect, in such case the participant can stay on study.
  - For participants with equivocal results even on the next scheduled restaging scan, the scan can be repeated again at a subsequent protocol scheduled assessment or sooner, although surgery or use of an advanced imaging modality are encouraged. Surgical pathology can be obtained via biopsy or resection.
- For lesions treated by stereotactic radiosurgery, additional evidence of tumor progression or treatment effect (radionecrosis) can be acquired with an advanced imaging modality, such as perfusion MRU; magnetic resonance spectroscopy, or 18FLT PET. In addition, clinical judgment and involvement of a multidisciplinary team may be required to adjudicate and distinguish between radiation necrosis and true progression. Note, that these advanced imaging modalities have not been extensively studied with regards to immunotherapy-based approaches and therefore cannot be recommended to distinguish between tumor progression and immune-related changes at present.
  - Irrespective of the additional testing obtained, if subsequent testing shows that progression has occurred, the date of progression should be recorded as the date of the scan at which this issue was first raised.
- Participants can also have an equivocal finding on a scan (e.g., as small lesion that is not clearly new).
  - Continued treatment is permissible until the next protocol-scheduled assessment.
  - If the subsequent assessment shows that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

16.2.2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, each lesion is classified at baseline as either a target or a non-target lesion:

Target lesions

All measurable lesions up to a maximum of five CNS lesions should be identified as target lesions and recorded and measured at baseline using the longest diameter. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and for reproducibility of measurement. Each target lesion must be uniquely and sequentially numbered on the eCRF.

For participants with recurrent disease who have multiple lesions, of which only one to two are increasing in size, the enlarging lesions should be prioritized as target lesions for the response assessment. If lesions not previously treated with local therapies are present, these are preferred for selection as target lesions. Lesions with prior local treatment (i.e., stereotactic radiosurgery or surgical resections) can be considered measurable if progression has occurred since the time of local treatment and if they are > 5 mm in diameter.

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

Non-Target lesions

All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required for non-target lesions and these lesions should be classified as present, absent or unequivocal progression during follow-up assessments. Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on the eCRF.

Documentation of previously treated lesions

For previously treated target or non-target lesions, the previous treatment should be documented (e.g. stereotactic radiosurgery, whole brain radiotherapy, surgical resection) on the Prior antineoplastic therapy eCRF pages.

16.2.2.4 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 for the target (Table 16-6) and non-target lesions (Table 16-7) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-8) as well as the presence or absence of new lesions, corticosteroid usage relative to baseline, ECOG performance scale and other clinical evaluation findings relative to baseline.

16.2.2.4.1 Follow-up and recording lesions

At each visit and for each lesion the actual date of the MRI 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/local reader in order to derive the overall visit response.

16.2.2.4.2 Determination of response/progression

The evaluation of overall intracranial lesion response at each assessment is a composite of the target lesion response, non-target lesion response, the presence of new lesions, corticosteroid usage relative to baseline, and clinical status as assessed by investigator and supported by the ECOG Performance Scale relative to baseline.

Participants (except participants with leptomeningeal disease, see Section 16.2.3.4) who have measurable and/or non-measurable disease in the brain at baseline and have received at least one dose of therapy will be considered evaluable for response.

All target lesion or non-target lesions must be assessed using the same methods and techniques as baseline for CR/PR/SD.

Determination of target lesion response

Target lesions should be assessed quantitatively at each of the time points specified in the protocol.

Table 16-6 Response assessment of target lesions

Response Criteria	Evaluation of target lesions
Complete response (CR)	Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and participant is stable or improved clinically.
Partial response (PR)	At least a 30% decrease in the sum of longest diameters of CNS target lesions, taking as reference the baseline sum of longest diameters sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
Progressive disease (PD)	At least a 20% increase in the sum of longest diameters of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.
Stable disease (SD)	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.
Not evaluable (NE)	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

Determination of non-target lesion response

Non-target lesions should be assessed qualitatively at each of the time points specified in the protocol.

Table 16-7 Response assessment of non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete response (CR)	Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
Non-complete response or non-progressive	Persistence of one or more non-target CNS lesion or lesions.

Response Criteria	Evaluation of non-target lesions
disease (Non-CR/non-PD)	
Progressive disease (PD)	Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.
Not evaluable (NE)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different technique than baseline

New lesions

New lesions can appear during treatment. The finding of a new CNS lesion should be unequivocal and not due to technical or slice variation. A lesion not present at baseline and appearing at any follow-up evaluation timepoint is considered a new lesion.

If the MRI is obtained with slide thickness of 1.5 mm or less, the new lesion should also be visible in axial, coronal and sagittal reconstructions of 1.5 mm or thinner projections. If a new lesion is equivocal, for example because of its small size (i.e., $\leq$ 5 mm), continued therapy can be considered, and a follow-up assessment will clarifiy if it really is new disease. If repeated scans confirm a new lesion, progression should be declared using the date of the initial scan showing the new lesion. In the case of immunotherapy-based treatment, however, new lesions alone may not constitute progressive disease.

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 eCRF page.

Corticosteroids

The corticosteroids (including medication name, dose and unit, frequency, route, start and end date, indication, ongoing, status compared to baseline) used for response determination have to be recorded in the eCRF.

The corticosteroids dose at the time of the tumor assessment will be compared with the dose taken at the time of the baseline tumor assessment. If the participant is not taking corticosteroids at baseline, a zero dose will be considered as the baseline value. If corticosteroids dose is not available at baseline, then the baseline dose will be considered unknown. Every effort should be made to document the baseline and subsequent corticosteroid doses.

If corticosteroids information is not collected at the intracranial assessment, the most recently recorded corticosteroid dose will be considered.

In the absence of clinical deterioration related to the tumor, an increase in corticosteroid dose alone should not be used as a sole determinant of progression. Participants with stable imaging results and whose corticosteroid dose has increased for reasons other than clinical deterioration related to the tumor do not qualify as having stable disease or progression. These participants should be observed closely, and if their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease, but if further clinical deterioration related to the tumor becomes apparent they will be considered as having progression. The date of progression should be the first time point at which corticosteroid dose increase was necessary.

Clinical Status

Clinical performance status will be evaluated based on the investigators' opinion and complemented by the ECOG performance status scale. At each protocol-specified time point, ECOG assessment should occur and intracranial tumor assessment should be coincident with ECOG assessment.

Clinical status based on the investigators' opinion used for response determination has to be recorded in the eCRF page.

If ECOG is unknown or not done at the intracranial tumor assessment, the previous ECOG assessment could be used for determination of the response.

16.2.2.4.3 Evaluation of overall lesion response

The evaluation of overall intracranial lesion response at each assessment is a composite of the target lesion response, non-target lesion response, the presence of new lesions, corticosteroid use relative to baseline, and clinical status as assessed by investigator and supported by the ECOG Performance Scale as shown below in Table 16-8.

Table 16-8 Overall Lesion Response at each assessment

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
Target Lesions	None	≥ 30% decrease in sum LD relative to baseline	< 30% decrease relative to baseline but <20% increase in sum LD relative to nadir #	≥ 20% increase in sum LD relative to nadir #
Non-target Lesions §	None	Stable or improved	Stable or improved	Unequivocal PD*
New Lesion(s) †	None	None	None	Present *
Corticosteroids compared to baseline	None	Stable or decreased	Stable or decreased	Not applicable ‡
Clinical Status compared to baseline	Stable or Improved	Stable or improved	Stable or improved	Worse*
Requirement for Response	**All**	**All**	**All**	**Any ‡**

Nadir: the smallest sum of diameter of all target lesions recorded at or after baseline

§ Non-target lesions response: stable (Non-CR/Non-PD), improved (CR)

* progression occurs when this criterion is met

† A new lesion is one that was not present on prior scans and is visible in minimum two projections.

If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease.

If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression.

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease

‡ Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration (see Section 16.2.2.4.2).

Sum LD: sum of longest diameters

Not evaluable (NE) overall lesion response is described in Section 16.2.2.4.3

Corticosteroids (see Section 16.2.2.4.2) and clinical status based on the investigators' opinion (see Section 16.2.2.4.2)

Complete response (CR)

All of the following criteria must be met:

1. Complete disappearance of all enhancing target and non-target lesions, sustained for at least 4 weeks. In the absence of a confirmatory MRI 4 weeks after the criteria for response are met, this evaluation will be considered at best stable disease.
2. No new lesions.
3. Participants must either be on no corticosteroids or on physiologic replacement doses only.
4. Stable or improved clinical status per investigator supported ECOG performance status scale compared to baseline.

Partial response (PR)

All of the following criteria must be met:

1. Greater than or equal to 30% decrease from baseline in the sum of longest diameters of all target lesions sustained for at least 4 weeks. In the absence of a confirmatory scan 4 weeks after the criteria for response are met, this evaluation will be considered at best stable disease.
2. Stable or improved non-target lesions.
3. No new lesions.
4. The corticosteroid dose at the time of the scan evaluation is not greater than the corticosteroid dose at the time of the baseline MRI scan.
5. Stable or improved clinical status per investigator supported ECOG performance status scale compared to baseline.

Stable disease (SD)

All of the following criteria must be met:

1. Less than 30% decrease from baseline but less than 20% increase from nadir in the sum of longest diameters of all target lesions.
2. Does not qualify for CR, PR, or PD.
3. No new lesions.
4. The corticosteroid dose at the time of the scan evaluation is not greater than the corticosteroid dose at the time of the baseline MRI scan.
5. Stable or improved clinical status per investigator supported ECOG performance status scale compared to baseline.

Progressive disease (PD)

Any of the following criteria must be met:

1. Greater than or equal to 20% increase in the sum of longest diameters of all target lesions relative to nadir.
2. Unequivocal progression of non-target lesions. To achieve unequivocal progression on the basis of non-target disease there must be an overall level of substantial worsening on the NT disease such that, even in the presence of CR, PR, or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
3. Any new lesion.
4. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection etc.). The definition of clinical deterioration is at the discretion of the investigator, however, it is recommended that a decline in the ECOG performance status, for at least 7 days, be considered a clinical deterioration unless attributable to co-morbid events or changes in corticosteroid dose.
   a. Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.
5. Failure to return for evaluation due to death or deteriorating condition unless caused by documented non-related disorders.

Not evaluable status (NE)

1. Progressive disease has not been documented and one or more target or non-target lesions have not been assessed.
2. Change in method or technique for assessing target and non-target lesions from baseline regardless of the justification of the change. E.g. if a participant develops a contraindication to MRI intravenous (IV) contrast media during the trial, a non-contrast MRI of the brain can be used (if possible); the participants response should only be recorded as Not evaluable unless there is progressive disease.

16.2.2.4.4 CNS and non-CNS Response Assessment

At each protocol-specified time point, a response assessment should occur and intracranial assessment should be coincident with extracranial and whole body assessment. Table 16-9 shows CNS and non-CNS response assessment.

Note that progressive disease in either compartment (namely, intracranial or extracranial compartments) is considered progressive disease overall. Table 16-6 shows the additional corticosteroid and clinical status requirements to deem a partial response or a complete response.

Table 16-9 CNS and non-CNS response assessment

CNS (RANO-BM)	Non-CNS (RECIST 1.1)
Complete response, partial response or stable disease (or non-CR/Non-PD)	Complete response, partial response or stable disease (or non-CR/Non-PD)
Complete response, partial response or stable disease (or non-CR/Non-PD)	Progressive Disease

CNS (RANO-BM)	Non-CNS (RECIST 1.1)
Progressive Disease	Complete response, partial response or stable disease (or non-CR/Non-PD)
Progressive Disease	Progressive Disease

16.2.3 Efficacy definitions

16.2.3.1 Best overall intracranial response

The best overall intracranial response (BOIR) is the best intracranial response recorded from the randomization/start of treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the randomization/treatment started) and will be determined programmatically based on the investigator/local reader's assessment of response at each time point.

The best overall intracranial 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 intracranial 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 intracranial response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall intracranial 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.

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 in which intracranial response is the primary endpoint, confirmation of partial response or complete response at least 4 weeks later is necessary to deem either one the best overall intracranial response.

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

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

- PD = progression ≤ 12 weeks after randomization/start of treatment (and not qualifying for CR, PR or SD).
- Not evaluable (NE) = 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)

The time durations specified in the SD/PD/NE definitions above are defaults based on a 6-8 week tumor assessment frequency. However these may be modified for specific indications (to be more or less aggressive). In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

16.2.3.2 Endpoints

Based on the participants' best overall intracranial response during the study, the following endpoints are then calculated:

Overall intracranial response rate (OIRR) is the proportion of participants with a confirmed best overall intracranial response (BOIR) of CR or PR.

Intracranial Disease control rate (IDCR) is the proportion of participants with a confirmed BOIR of CR or PR or SD (or non-CR/Non-PD).

Duration of intracranial response (DOIR): DOIR only applies to participants whose confirmed BOIR is CR or PR. DOIR is defined as time from first documented intracranial response of either CR or PR to the date of the first documented intracranial progression or date of death due to any cause. Participants will be censored if they have disease progression in organs other than brain and have no scans in brain after that. The censoring date will be the date of the last adequate tumor assessment in brain.

Time to intracranial response (TTIR): TTIR is defined as the time from the date of randomization/start of the treatment to the date of the first documented intracranial response of either CR or PR, which must be subsequently confirmed (date of initial response is used, not date of confirmation).

All participants will be included in TTIR calculations. Participants without a confirmed intracranial CR or PR will be censored at the study-maximum follow-up time (i.e. LPLV−FPFV) for participants with event (intracranial progression or death due to any cause), or at the date of the last adequate intracranial tumor assessment for participants without an event.

16.2.3.3 Definitions of dates

Assessment dates

For each assessment, the **assessment date** is calculated as the latest of all measurement dates if the overall lesion response at that assessment is CR/PR/SD/NCRNPD/NE. Otherwise – if overall lesion response is progression – the assessment date is calculated as the earliest date of all measurement dates at that visit.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

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 / PR when this status is later confirmed. The date of initial response is used, not date of confirmation.

End dates

The dates which are used to calculate endpoints are defined as follows:

- Date of death due to any cause is the date of death due to "Study indication" or "Other".
- Date of intracranial progression is the first assessment date at which the overall lesion response was recorded as progressive disease in the brain.
- Date of last adequate intracranial tumor assessment is the date the last tumor assessment in brain with overall lesion response of CR, PR or SD 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 in brain are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.

Secondary anti-cancer therapy date

The date which is used for BOIR determination is defined as follows:

- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy, radiotherapy, or surgery.

16.2.3.4 Handling of participants with only non-measurable disease at baseline

It is possible that participants with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. enrollment, type of disease such as leptomeningeal disease). 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 participants with only non-measurable disease at baseline should be included in the main analysis (Intent-To-Treat approach) 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 with only non-measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 16-10.

Table 16-10 Overall Lesion Response at each assessment: Participant with only non-target disease at baseline

Criteria	Complete Response	Non-CR/Non-PD	Progressive Disease
Non-target Lesions §	None	Stable or improved	Unequivocal PD*
New Lesions †	None	None	Present *
Corticosteroids compared to baseline	None	Stable or decreased	Not applicable ‡
Clinical Status compared to baseline	Stable or Improved	Stable or improved	Worse*
Requirement for Response	All	All	Any ‡

§ Non-target lesions response: stable (Non-CR Non-PD), improved (CR)

* Progression occurs when this criterion is met.

† A new lesion is one that not present on prior scans and is visible in minimum two projections.

If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease.

If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression.

‡ Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration (see Section 16.2.2.4.2).

Not evaluable (NE) overall lesion response is described in Section 16.2.2.4.3

Corticosteroids (see Section 16.2.2.4.2) and clinical status based on the investigators' opinion (see Section 16.2.2.4.2)

16.2.3.4.1 Evaluation of overall lesion response

Complete response (CR)

All of the following criteria must be met:

1. Complete disappearance of all non-target lesions, sustained for at least 4 weeks. In the absence of a confirmatory MRI 4 weeks after the criteria for response are met, this evaluation will be considered at best Non-CR/Non-PD.
2. No new lesions.
3. Participants must either be on no corticosteroids or on physiologic replacement doses only.
4. Stable or improved clinical status per investigator supported ECOG performance status scale compared to baseline.

Non-CR/Non-PD

All of the following criteria must be met:

1. Does not qualify for CR or PD.
2. No new lesions.

3. The corticosteroid dose at the time of the scan evaluation is not greater than the corticosteroid dose at the time of the baseline MRI scan.
4. Stable or improved clinical status per investigator supported ECOG performance status scale compared to baseline.

Progressive disease (PD)

Any of the following criteria must be met:

1. Unequivocal progression of non-target lesions. To achieve unequivocal progression on the basis of non-target disease there must be an overall level of substantial worsening on the NT disease.
2. Any new lesion.
3. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection etc.). The definition of clinical deterioration is at the discretion of the investigator, however, it is recommended that a decline in the ECOG performance status, for at least 7 days, be considered a clinical deterioration unless attributable to co-morbid events or changes in corticosteroid dose.
   a. Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.
4. Failure to return for evaluation due to death or deteriorating condition unless caused by documented non-related disorders.

16.2.3.4.2 Best overall intracranial response

The best overall intracranial response for each participant 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
- Non-CR/Non-PD = at least one Non-CR/Non-PD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR)
- PD = progression ≤ 12 weeks after randomization/start of treatment (and not qualifying for CR or Non-CR/Non-PD).
- Not evaluable (NE) = all other cases (i.e. not qualifying for confirmed CR and without Non-CR/Non-PD after more than 6 weeks or early progression within the first 12 weeks)

16.2.4 References

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