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Novartis Research and Development

INC280/Capmatinib

Clinical Trial Protocol CINC280A2301 / NCT04427072

A phase III, randomized, controlled, open-label, multicenter, global study of capmatinib versus SoC docetaxel chemotherapy in previously treated patients with EGFR wt, ALK negative, locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC harboring MET exon 14 skipping mutation (METΔex14)

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
AJCC	American Joint Committee on Cancer
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANC	Absolute Neutrophil Count
ART	Anti-Retroviral Treatment
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate Aminotransferase
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
b.i.d.	bis in die/twice a day
BAL	Bronchoalveolar Lavage
BCG	Bacille Calmette-Guerin
BCRP	Breast Cancer Resistance Protein
BIRC	Blinded Independent Review Committee
BOIR	Best Overall Intracranial Response
BOR	Best Overall Response
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 Day 1
CDNa	Complementary Deoxyribonucleic Acid
CI	Confidence Interval
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus Disease 2019
CLIA	Clinical Laboratory Improvement Amendments
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
CR	Complete Response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria Adverse Event

[redacted]

[redacted]	[redacted]
CV	Coefficient of Variation
CYP1A2	Cytochrome P450 1A2
CYP3A	Cytochrome P450 3A
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DDE	Direct Data Entry
DDI	Drug-Drug Interaction
DIDB	Drug Interaction Database
DILI	Drug-Induced Liver Injury
DLCO	Diffusing capacity of the Lungs for Carbon monoxide
DLT	Dose Limiting Toxicity
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 Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
EOT	End Of Treatment
EQ-5D-5L	EuroQoL-5 Dimension-5 Level
ERCP	Endoscopic retrograde cholangiopancreatography
eSource	Electronic Source
ET	Extension Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose- Positron Emission Tomography
FFPE	Formalin Fixed Paraffin Embedded
FPFV	First Patient First Visit
FSH	Follicle Stimulating Hormone
FUP	Follow-Up Period
G-CSF	Granulocyte Colony-Stimulating Factor
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HAV	Hepatitis A Virus
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus

[redacted]

HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HER2	Human Epidermal growth factor Receptor 2
Hgb	Hemoglobin
HGF	Hepatocyte Growth Factor
HIV	Human immunodeficiency virus
hr	Hour
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSV	Herpes Simplex Virus
i.v.	intravenous
IB	Investigator's Brochure
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
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ILD	Interstitial Lung Disease
IN	Investigator Notification
INR	International Normalized Ratio
IO	Immuno-Oncology
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LPLV	Last Patient Last Visit
MAP	Managed Access Program
MATE	Multidrug And Toxin Extrusion
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
METΔex14	MET exon 14 skipping
MET	Mesenchymal Epithelial Transition factor
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
[redacted]	[redacted]
NSCLC	Non-Small Cell Lung Cancer
NTI	Narrow Therapeutic Index
NTKR	Neurotrophic Tyrosine Kinase Receptor

[redacted]

OIRR	Overall intracranial response rate
ORR	Overall Response Rate
OS	Overall Survival
P-gp	Permeability-GlycoProtein
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PD-1	Programmed cell Death protein 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
[redacted]	[redacted]
PFT	Pulmonary Function Test
PK	Pharmacokinetic(s)
PLT	Platelet
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
QTcF	QT interval corrected by Fridericia's formula
R value	ALT/ALP x ULN
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RANKL	Receptor Activator of Nuclear factor Kappa-B Ligand
RECIST	Response Evaluation Criteria In Solid Tumors
RET	Rearranged during transfection
RNA	Ribonucleic Acid
ROS1	c-ros oncogene 1
RP2D	Recommended phase two 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
SoC	Standard of Care
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
TKIs	Tyrosine Kinase Inhibitors
TSH	Thyroid Stimulating Hormone
TTE	Time To Event
TTIR	Time To Intracranial Response
TTR	Time To Response
Ty21a	Live-attenuated TY2 strain of Salmonella Typhi

[redacted]

ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale
VATS	Video-assisted thoracic surgery
WHS	White coat Syndrome
WoC	Withdrawal of Consent
wt	Wildtype

[redacted]

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 Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
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, 75 mg twice a day)
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 paper source forms used at the point of care
End of the study	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
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.
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to Novartis and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, an 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.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.

[redacted]

Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or 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.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
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
Remote	Describes any trial activities performed at a location that is not the investigative site
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 in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the study	The start of the study 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
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
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.

[redacted]

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.

[redacted]

Amendment 2 (24-Feb-2022)

Amendment rationale

As of the release date of this amendment, 21 participants have been randomized in this study.

This amendment addresses the following revisions:

- MET mutation status: to allow also local results from a validated test according to local regulation and documented as part of the participant's medical record, to be used for participant eligibility.
- SAE reporting: immediate reporting clarified to align with Health Authority (especially with Federal Institute for Drugs and Medical Devices (BfArM)) requirements.

Changes to the protocol

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

The following sections of the protocol were changed:

- List of abbreviations
  - Relevant abbreviations were added or updated.
- Glossary of terms
  - Relevant terms were added or updated.
- Protocol summary
  - Updated to reflect the changes made in this protocol amendment.
- Section 1.1 Background
  - Update of new molecular targets as oncogenic drivers
  - New references added.
- Section 1.1.1.1 Non-clinical experience
  - New reference added.
- Section 1.1.1.2 Clinical experience
  - Data from latest [capmatinib Investigator's Brochure] V.13 included.
  - Information on co-administered MATE substrate exposure added.
- Section 2 Objectives, endpoints and estimands
  - Secondary objective related to the characterization the pharmacokinetics of capmatinib in this study population updated to specify that it will be assessed by plasma concentrations at specific time points only.
  - Secondary objective related to the assessment of the effect of capmatinib versus docetaxel on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL) updated to clarify that time to symptom deterioration will be analyzed by treatment group for chest pain, cough and dyspnea scores per QLQ-LC13 as well as global health status/QoL per QLQ-C30 questionnaire but not per EQ-5D-5L.

[redacted]

[redacted]

- Section 3 Study design
  - Sentence added to specify that additional participants may be randomized to support the analysis of the second supplementary estimand.
  - Clarification added that all participants will enter in survival follow-up following the completion of all study assessments (as applicable).
  - Figure 3-1 study design updated to move the METΔex14 mutation status into the Study population / Eligibility box. Patient reworded to participant to align with standard language. Extension (E1) typo corrected to Extension (ET).
  - Pre-screening: sentence added to clarify that all participants must sign the molecular pre-screening ICF, regardless of if they have a local METΔex14 mutation positive result or if they will be submitting a tumor sample for central pre-screening by the Novartis-designated laboratory for determination of their METΔex14 mutation status.
  - Survival Follow-up: sentence corrected to clarify that after study treatment discontinuation or post-treatment follow-up phase discontinuation (as applicable), participant will enter in survival follow-up, irrespective of reasons of discontinuations.
- Section 4.1 Rationale for study design
  - Clarification added that the study will enroll participants with locally advanced/metastatic NSCLC, which are EGFR wt for EGFR mutations that predict sensitivity to EGFR therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations.
  - Participants must be docetaxel naive and candidates for single agent chemotherapy (docetaxel) and progressed on or after the last therapy before study entry. Participants with other druggable targetable oncogenic drivers such as BRAF, ROS1, RET, NTRK and KRAS will be excluded.
- Section 4.5 Risks and benefits
  - Paragraph on investigational risk included.
- Section 4.5.2 Docetaxel
  - Section updated as per latest docetaxel SmPC dated 17-Apr-2020.
- Section 5.1 Inclusion criteria
  - Inclusion criteria 4: updated to allow METΔex14 mutation assessment per a locally performed, tissue-based test which is validated according to local regulation, from a Clinical Laboratory Improvement Amendments (CLIA)-certified US laboratory or an accredited local laboratory outside of the US. The positive METΔex14 mutation result as determined per local test must be documented in the participant's source documents and in the CRF prior to entering main screening.
  - Inclusion criteria 5: updated to clarify that the tumor tissue sample must be provided with sufficient quality (as defined in the study [laboratory manual]) to allow the assessment of METΔex14 mutation status. The provision of the tumor tissue sample is

[redacted]

mandatory for all participants, including those who have a METΔex14 mutation result from a local test.

- Inclusion criteria 6: updated to clarify that participants must be docetaxel naive and participants must have progressed on or after the last therapy before study entry to be eligible.
- Inclusion criteria 12: new criteria added for participants to have a life expectancy of at least 3 months to align with the program standard language.

- Section 5.2 Exclusion criteria
  - Exclusion criteria 5: list of examples of druggable molecular alterations updated.
  - Exclusion criteria 15: updated to include HIV participants only when the disease is under control, the suppressed viral loads as defined by local guidelines and on established anti-retroviral treatment (ART) for at least four weeks prior to enrollment
  - Exclusion criteria 18: separation of the definition of post-menopausal women and women of no child-bearing potential for more clarity.
  - Exclusion criteria 20: new exclusion criteria added to include requirement for specific timing of receiving a live vaccine prior to starting study treatment.
- Section 6.1.2 Additional study treatments
  - Sentence added to confirm that no other treatment beyond investigational drug (capmatinib) and control drug (docetaxel) are included in this trial.
  - Docetaxel administration information removed from this section as already available in Section 6.7.2.2.
- Section 6.1.5.2 Crossover to capmatinib therapy
  - Clarification added that for participants who discontinue docetaxel for reasons other than BIRC confirmed disease progression (such as treatment intolerance, AEs…), safety and efficacy tumor assessments and PROs collection must continue to be performed while waiting to confirm crossover eligibility.
  - Clarification added that participants who crossover from the docetaxel arm to capmatinib will have imaging assessments performed according to local practice and institutional guidelines; the disease progression on capmatinib treatment in ET will be determined based on investigator assessment only. When these participants permanently discontinue treatment with capmatinib, they must complete the ET-EOT visit and all these participants will then be followed for safety until 30 days after the last dose of capmatinib.
- Section 6.2.1 Concomitant therapy
  - During the entire duration of the study no anticancer therapies other than the study medication should be given to participants with the exception of radiation as allowed per protocol.
- Section 6.2.2 Prohibited medication
  - Live vaccines (including Coronavirus Disease 2019 (COVID-19) live vaccine) added to the list of prohibited medication.
- Section 6.5.3.1 Follow-up on potential drug-induced liver injury cases
  - Testing of Glutamate Dehydrogenase (GLDH) changed from required to recommended.

[redacted]

- Section 6.7 Preparation and dispensation
  - Updated to mention that 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, each capmatinib shipment/provisioning of will be for a maximum of 3-month supply.
- Section 6.7.1.1 Handling of study treatment
  - Sentence added to clarify that the investigator must provide accountability also for locally sourced materials used for administration (e.g. i.v. bags).
  - Sentence added to allow flexibility for return or destruction of unused drug at sites.
- Section 7 Informed consent procedures
  - Updated to clarify that information about common side effects already known about the investigational treatment should be discussed with the participant upon obtaining consent and also during the study as needed.
- Section 8 Visit schedule and assessments
  - Table 8-1 Allowable window for participant assessments corrected: windows allowed for PROs assessments is within 3 days prior to the visit during the treatment and until progression and ±7 days of the visit for EOT and post-progression timepoints.
  - Clarification added that participants who discontinue from study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.
  - Clarification added that participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree.
  - Table 8-2 Assessment schedule split into 2 separate tables for more clarity: Table 8-2 for all participants from pre-screening to survival and Table 8-3 for docetaxel participants who crossover to capmatinib arm. Collection of PD-L1 status as per participant's record added in Table 8-2. Due to the split of the assessment schedule into 2 tables, all subsequent table numbers in Section 8 have been updated.
- Section 8.1 Molecular pre-screening
  - Section updated to allow METΔex14 mutation assessment per a locally performed, tissue-based test which is validated according to local regulation or per Novartis-designated central laboratory test.
  - Clarification added related to tumor sample requirement for METΔex14 testing. The quality/quantity of tumor samples will be determined at the Novartis-designated central laboratory. Tumor samples must contain at least 10% tumor content and the minimum effective tumor area specified in the study [laboratory manual].
  - Clarification added on the purpose of blood sample collected at pre-screening: potential development of liquid biopsy *in vitro* diagnostic test(s), such as companion diagnostic.
  - Clarification added on tumor requirement in case of ALK testing not available locally.
  - Clarification added on the purpose to retain remaining tissue from all participants: potential development of *in vitro* diagnostic test(s), such as companion diagnostic test(s).

[redacted]

- Section 8.2 Screening
  - Sentence about central confirmation of METΔex14 mutation to be completed prior to randomization for all participants removed.
- Section 8.2.2 Information to be collected on screening failures
  - Collection of PD-L1 status as per participant's record added to the information to be collected on screening failures.
- Section 8.3 Participant demographics/other baseline characteristics
  - Collection of baseline PD-L1 tumor status added to data to be collected on participant characteristics at screening.
- Section 8.4.1 Tumor imaging assessments
  - Clarifications on data transmitted to the imaging CRO via baseline clinical form and cytology form were added.
- Section 8.4.1.3 Confirmation of disease progression by BIRC
  - Sentence added to clarify that for participants who crossed-over from the docetaxel arm to capmatinib arm, capmatinib will count as next-line of therapy.
- Section 8.4.3 Overall Survival
  - Updated to clarify that all participants will enter the survival follow-up period once they complete all study assessments per protocol, as applicable.
- Section 8.5.1 Laboratory evaluations
  - Sentence added to specify that during a public health emergency as declared by local or regional authorities, 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.
- Section 8.6.1 Clinical Outcome Assessments (COAs)
  - Allowable window for participant assessments corrected: windows allowed for PROs assessments is within 3 days prior to the visit during the treatment and until progression and ±7 days of the visit for EOT and post-progression timepoints.
  - Collection of PROs during treatment and efficacy follow-up, as well as post-progression phase was better described.
  - Clarification added that for participants who discontinue docetaxel treatment and enter extension treatment, PROs will be collected only at 6, 12 and 18 weeks (±7 days) post-docetaxel treatment progression by telephone interview or by face to face interview in the event participant is at site to perform other assessments. There won't be any possibility to collect data on electronic device.
- Section 8.6.3.1 Biomarkers assessments in tumor
  - Clarification added that tumor samples must be provided with sufficient quality and quantity to allow the central assessment of MET mutation status for all participants and for potential development of in vitro diagnostic test(s), such as companion diagnostic test(s). [redacted]

[redacted]

  - In addition, tumor samples must contain a minimum effective tumor area per slide as described in the study [laboratory manual] and as required for the central assessment of MET mutation status. Samples obtained from bone metastases and cytology samples are not acceptable.
- Section 9.1.1 Discontinuation from study treatment
  - Discontinuation language updated as per protocol template V5.0.
- Section 9.1.2 Discontinuation from study
  - New section added for clarity and language updated as per protocol template V5.0.
- Section 9.2 Withdrawal of informed consent/Opposition to use date/biological samples
  - Withdrawal language updated as per protocol template V5.0.
- Section 9.3.3 Survival follow-up
  - Updated to clarify that participants will enter the survival follow-up period once they complete the 30-day safety follow-up and/or efficacy follow-up (if applicable) after treatment discontinuation (whichever is longer) and the post-progression PRO follow-up.
- Section 10.1.3 SAE reporting
  - Immediate reporting clarified and to align with Health Authority requirements and especially with Federal Institute for Drugs and Medical Devices (BfArM) requirements.
- Section 10.1.4 Pregnancy reporting
  - Language regarding Pregnant Participants and Pregnant Partners modified for clarity.
  - Sentence added to clarify that after consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.
- Section 10.1.2 Serious adverse events
  - Sentence added to clarify that all reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.
- Section 10.3 Committees
  - New section created / sections reorganized for clarity. Added an overarching Level 2 section header for the various study committees.
- Section 10.1.5 Reporting of study treatment errors including misuse/abuse
  - Updated to clarify that 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.
- Section 12.4.3 Handling of intercurrent events of primary estimand
  - Sentence added to clarify that PFS will take into account all PFS events irrespective of the start of new anti-cancer therapy (treatment policy strategy).
- Section 12.4.6 Supplementary analysis
  - Updated to include a further supplementary estimand with a target population of the subset of participants for whom the METΔex14 mutation was confirmed by the Novartis-designated central laboratory.
- Section 12.5.1.1 Key secondary estimand/endpoint

[redacted]

  - Updated to include a further supportive analysis: ORR by BIRC based on the subset of participants for whom the METΔex14 mutation was confirmed by the Novartis-designated central laboratory.
- Section 12.5.4 Patient reported outcomes
  - Updated to specify that the distribution of time to symptom deterioration will be analyzed by treatment group for chest pain, cough and dyspnea scores per QLQ-LC13 as well as global health status/QoL per QLQ-C30 questionnaire but not per EQ-5D-5L.
- Section 12.8.1 Primary endpoint(s)
  - Section updated to align with the wording from the Statistical Analysis Plan (SAP) template with standard language for oncology.

In a concern of homogenization, the wording RECIST 1.1-defined PD has been used consistently in the protocol.

Additional revisions including editorial changes were made throughout the protocol.

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.

[redacted]

Amendment 1 (16-Dec-2020)

Amendment rationale

As of the release date of this amendment, 1 patient has been randomized in this study.

This amendment addresses the following revisions:

- Collection of post-progression PROs in order to capture additional cancer related symptoms during this period
- Addition of mitigation procedures to ensure participant safety and trial integrity in relevant sections, in the event of Public Event emergencies (e.g., COVID-19 pandemic)
- The primary scientific question of interest and the primary estimand, especially the estimand attributes treatment, variable and intercurrent events, were rephrased to align with the capmatinib program protocol standard language
- The objective to compare the overall response rate of capmatinib and docetaxel has been set as key secondary objective. This endpoint would support the assessment of clinical benefit and the interpretation of the primary endpoint results.
- MET (and ALK, if applicable) testing while patient is still receiving anti-cancer therapy at pre-screening has been allowed to facilitate recruitment
- Novartis guidelines on Response Assessment in Neuro-oncology (RANO) for Brain Metastases (BM) have been added as Appendix 2 to the protocol to support the secondary endpoint assessing intracranial anti-tumor activity of capmatinib in participants with Central Nervous System (CNS) lesions by BIRC. The definitions of time to intracranial response (TTIR) and duration of intracranial response (DOIR) have been updated accordingly.

Changes to the protocol

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

The following sections of the protocol were changed:

- List of abbreviations
  - Relevant abbreviations were added
- Protocol summary
  - Secondary objective summary was updated to reflect changes to key secondary objectives and PRO endpoints
- Section 2 Objectives and endpoints
  - The comparison of the overall response rates per RECIST 1.1 by BIRC of capmatinib and docetaxel were moved from a secondary endpoint to the key secondary endpoint
  - Secondary endpoints for Patient Reported Outcome was updated in Table 2-1
- Section 2.1 Primary estimands
  - The primary scientific question of interest was rephrased to align with the internal capmatinib standard protocol language.
  - A justification for targeting the described treatment effect was added.

[redacted]

  - The attributes of the primary estimand were revised to align with the internal capmatinib standard protocol language:
    - Treatment was clarified: treatment includes newly started antineoplastic therapy, if any
    - Variable was more precisely defined
    - Intercurrent events were updated (addition of study treatment discontinuation and unforeseen intercurrent events, removal of antineoplastic therapy)
    - The summary measure was clarified (removal of confidence interval and addition of the test for PFS)
- Section 2.2 Secondary estimands
  - Scientific question of interest and estimand were formulated for the new key secondary endpoint
- Section 3 Study design
  - Patient-reported outcome modality and duration of collection was updated
- Section 4.5 Risks and benefits
  - Benefit-risk assessment in the event of a Public Health Emergency was added
- Section 4.6 Rationale for Public Health Emergency mitigation procedures
  - This new section was added to describe rationale for Public Health Emergency mitigation procedures
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action
  - Formatting was updated
  - "Drugs to be used with caution during coadministration with capmatinib" table was removed from this section and embedded in Section 16.3 Appendix 3
- Section 6.2.1.2 Use of bisphosphonates or RANKL inhibitor
  - Guideline on use of receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor was added
- Section 6.2.1.3 Permitted radiotherapy
  - Guideline on local bone radiotherapy was added
- Section 6.2.2 Prohibited medication
  - "Capmatinib: prohibited drugs" table was removed and embedded in Section 16.3 Appendix 3
- Section 6.4 Treatment blinding
  - Measures to minimize the potential impact of knowledge of treatment assignment were described
- Section 6.5.1 Dose modifications
  - Exceptions to grade 4 toxicities were defined
  - Grade 4 event was removed for fatigue/asthenia in Table 6-3 to align with CTCAE version 5.0
- Section 6.5.3 Follow-up for toxicities
  - The term "asymptomatic" was removed from the event Amylase or lipase ≥ CTCAE grade 3 in Table 6-4

[redacted]

- Section 6.7 Preparation and dispensation
  - A paragraph was added to describe home delivery of study drug in the event of a Public Health emergency
- Section 7 Informed consent procedures
  - Home Nursing consent was added, if applicable
  - A paragraph was added to describe alternative methods of conducting informed consent discussion in the event of a Public Health emergency
- Section 8 Visit schedule and assessments
  - A paragraph was added to describe alternatives to on-site visits in the event of a Public Health emergency
  - Table 8-2 Assessment schedule was updated:
    - Pregnancy test (urine) was deleted at C1D1 and ET-C1D1 to ensure consistency with Section 8.5.3
    - PROs collection was removed from the Extension Treatment period and added to the Survival Follow Up period at three time points (6, 12 and 18 weeks post-progression)
    - The term "food administration" was replaced by "food consumption" and collection for capmatinib arm only was specified. Footnote was added to clarify the information on food consumption to be collected.
    - PK blood collection was updated to clarify collection for capmatinib arm only
- Section 8.1 Molecular pre-screening
  - A paragraph was added to allow MET (and ALK, if applicable) testing while patient is still receiving anti-cancer therapy at pre-screening
- Section 8.2.2 Information to be collected on screening failures
  - A sentence that was repeated by mistake was deleted
- Section 8.4.1 Tumor imaging assessments
  - Reference to Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria was updated to reflect the inclusion of the guideline in the amendment as Appendix 2
  - A paragraph was added to describe collection of images in the event of a Public Health emergency
- Section 8.5 Safety
  - A paragraph was added to describe safety monitoring in the event of a Public Health emergency
- Section 8.5.3 Pregnancy and assessments of fertility
  - A paragraph was added to describe alternatives to on-site pregnancy testing in the event of a Public Health emergency
- Section 8.6.1 Clinical Outcome Assessments (COAs)
  - Collection of PROs during treatment and efficacy follow-up was better described
  - Collection of PROs during post-progression period was added and time points were defined
  - A paragraph was added to describe alternative methods of PROs collection in the event of a Public Health emergency

[redacted]

- Section 8.6.3.2 Biomarker assessments in blood
  - Table 8-9 Biomarker sample collection plan was updated
    [redacted]
- Section 9.2.1 Follow-up for safety evaluations
  - 30-day safety follow-up for participants who transfer to another Novartis clinical study or Novartis treatment setting was clarified
- Section 12.1.4 Pharmacokinetic analysis set
  - It was clarified that concentration measurements need to be evaluable for steady state
- Section 12.4.2 Statistical model, hypothesis, and method of analysis
  - A sentence that was repeated was deleted
- Section 12.4.3 Handling of remaining intercurrent events of primary estimand
  - Language about discontinuation of study treatment for any reason before a PFS event was updated
  - Language about unforeseen intercurrent events (e.g., related to a Public Health emergency like the COVID-19 pandemic) was added
  - Start of new anti-cancer therapy was deleted as intercurrent event
- Section 12.4.6 Supplementary analysis
  - A paragraph to define a supplementary estimand was added to analyze the randomized treatment without any antineoplastic therapy post randomization
- Section 12.5 Analysis of secondary endpoints/estimands
  - Section title was updated
- Section 12.5.1 Efficacy endpoints
  - The section was split into two subsections. The first subsection describes the analysis for the key secondary efficacy endpoint, ORR by BIRC assessment, and includes a supportive analysis of ORR by investigator assessment. The second subsection contains the analyses for the other secondary endpoints as before.
  - In the definition of duration of response it was clarified that death means death due to any cause
  - For the endpoints DOIR and TTIR the event definition was changed to take into consideration death due to any cause to align with an updated version of the RANO-BM guideline (Appendix 2). The censoring of DOIR for death due to other causes than intracranial was deleted.
- Section 12.5.2 Safety endpoints
  - A paragraph that was repeated by mistake was deleted
- Section 12.5.4 Patient reported outcomes
  - An analysis of time to deterioration of symptom scores was added
- Section 12.8.2 Secondary endpoint(s)
  - This section was added to estimate the power for key secondary endpoint for the chosen sample size
- Section 15 References

[redacted]

  - Two new references were added
- Section 16.2 Appendix 2: Guidelines for Response Assessment in Neuro-oncology (RANO) for Brain Metastases (BM)
  - The Guidelines for RANO-BM was embedded to the protocol as Appendix.
- Section 16.3 Appendix 3: List of concomitant medications for patients on capmatinib
  - This appendix was added to summarize medications that require caution when used with capmatinib and prohibited drugs
  - A footnote related to the dose change required for certain permitted concomitant therapies requiring caution when concomitantly used with capmatinib was added

Additional revisions including editorial changes were made throughout the protocol.

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.

[redacted]

Protocol summary

Protocol number	CINC280A2301
Full Title	A phase III, randomized, controlled, open-label, multicenter, global study of capmatinib versus SoC docetaxel chemotherapy in previously treated patients with EGFR wt, ALK negative, locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC harboring MET exon 14 skipping mutation (METΔex14)
Brief title	Study of efficacy of capmatinib in comparison with standard of care docetaxel as a second or third line therapy in participants with non-small cell lung cancers harboring MET exon 14 skipping mutation.
Sponsor and Clinical Phase	Novartis, Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To date, no approved therapy for advanced MET mutated non-small cell lung cancer (NSCLC) pre-treated with one or two prior lines of systemic therapy exists. Capmatinib is an orally bioavailable, highly potent and selective MET inhibitor in biochemical and cellular assays and capable of blocking MET activation. Clinical data demonstrate that capmatinib monotherapy has anti-tumor activity in EGFR wt NSCLC harboring MET mutation. Safety data demonstrate that capmatinib is well tolerated by the target population at the dose of 400 mg b.i.d. (tablet).
Primary Objective(s)	The primary objective of this study is to compare the efficacy of capmatinib versus docetaxel by comparing progression-free survival (PFS) by blinded independent review committee (BIRC) according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 between treatment arms. The primary clinical question of interest is: what is the relative effect of the two treatment strategies in prolonging time to radiological progression by BIRC per RECIST 1.1 or death due to any cause in locally advanced or metastatic NSCLC harboring MET exon 14 skipping mutation, regardless of study treatment discontinuation or start of new antineoplastic therapy?
Secondary Objectives	Key secondary • To compare the overall response rates (ORR) per RECIST 1.1 by BIRC of capmatinib and docetaxel Secondary • To assess the antitumor activity of capmatinib versus docetaxel by evaluating duration of response, time to response and disease control rate by both BIRC and investigator according to RECIST 1.1 in both treatment arms and by evaluating ORR and PFS by investigator according to RECIST 1.1 in both treatment groups • To evaluate overall survival in participants treated with capmatinib versus docetaxel • To evaluate the safety profile of capmatinib versus docetaxel based on the incidence of adverse events and serious adverse events, change in vital signs, laboratory results and ECG in both treatment arms • To characterize the pharmacokinetics (PK) of capmatinib in this study population by assessing plasma concentrations at specific time points. • To assess the effect of capmatinib versus docetaxel on patient-reported disease-related symptoms, functioning, and health-related quality of life by evaluating the change from baseline in European Organization for Research and Treatment of Cancer (EORTC) QLQ-LC13, QLQ-C30, EuroQoL-5 Dimension-5 Level/EQ-5D-5L) questionnaires and time to symptom deterioration for chest pain, cough and dyspnea in the European Organization for Research and Treatment of Cancer (EORTC) QLQ-LC13 as well as global health status/QoL per QLQ-C30 questionnaire in both treatment groups • To assess intracranial anti-tumor activity of capmatinib and docetaxel in participants with Central Nervous System (CNS) lesions at baseline by BIRC by evaluating overall intracranial response rate, duration of intracranial response, time to intracranial

	response, intracranial disease control rate by BIRC as per RANO-BM criteria in both treatment arms.
Study design	This is a multicenter, open-label, randomized, active-controlled, global phase III study that will enroll adult participants with EGFR wt, ALK rearrangement negative, NSCLC harboring METΔex14 skipping mutations who have progressed on one or two prior lines of systemic therapy for locally advanced or metastatic stage and are candidates for docetaxel. The study will randomize approximately 90 participants globally. Participants eligible for the study will be randomized in a 2:1 ratio to one of the two treatment arms: capmatinib (investigational therapy) or docetaxel. The randomization will be stratified by prior lines of systemic therapy received for advanced/metastatic disease (one line vs. two lines). Participants randomized to docetaxel treatment will be eligible to crossover to receive capmatinib treatment after BIRC-confirmed, RECIST 1.1-defined progressive disease (PD) and after meeting the eligibility criteria prior to crossover. For all participants, the respective treatment (either with capmatinib or docetaxel) may be continued beyond initial disease progression as per RECIST 1.1 (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. After treatment discontinuation, all participants will be followed for safety evaluations during the safety follow-up period, and the participant's status will be collected every 12 weeks as part of the survival follow-up.
Study population	This study will randomize approximately 90 participants, male and female, aged 18 or older, with EGFR wt, ALK rearrangement negative, advanced (stage IIIB, IIIC or IV) NSCLC harboring METΔex14 mutations and who have progressed on one or two prior lines of systemic therapy for advanced/metastatic disease.
Key Inclusion criteria	• Stage IIIB/IIIC (not amenable to surgery, radiation or multi modality therapy) or IV NSCLC at the time of study entry. • Histologically or cytologically confirmed diagnosis of NSCLC that is EGFR wt (for 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 as assessed by a validated test as part of the participant's standard of care and has METΔex14 mutation determined by Novartis-designated central laboratory or by a locally performed, tissue-based test, validated according to local regulation. • At least one measurable lesion as defined by RECIST 1.1. • Participants must have progressed on one or two prior lines of systemic therapy for advanced/metastatic disease (stage IIIB/IIIC [not candidates for surgery, radiation or multi modality therapy] or IV NSCLC) and must be docetaxel naive and be candidates for single agent chemotherapy (docetaxel). Participants must have progressed on or after the last therapy before study entry • ECOG performance status of 0 or 1.
Key Exclusion criteria	• Prior treatment with any MET inhibitor or HGF-targeting therapy • Participants with known druggable molecular alterations (such as ROS1 and RET rearrangements, BRAF mutation, KRAS mutation, NTRK fusions, etc.) which might be a candidate for alternative targeted therapies. • Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention). • Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome. • Clinically significant, uncontrolled heart diseases
Study treatment	Capmatinib (INC280) or docetaxel

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Efficacy assessments	• Tumor assessment by RECIST 1.1 performed every 6 weeks (i.e. every 2 cycles) until disease progression as assessed by the investigator and confirmed by BIRC. • 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	Capmatinib PK will be assessed in participants who receive capmatinib treatment at the following time points: • Cycle 1 Day 15 • Cycle 3 Day 1
Key safety assessments	• Laboratory assessments, including hematology, chemistry, urinalysis, coagulation, hepatitis markers, HIV testing where locally required, pregnancy testing (for women of child-bearing potential) • Physical examination • Vital signs and body weight • Electrocardiogram (ECG) • Collection of Adverse Events (AE) and Serious Adverse Events (SAE)
Other assessments	• Patient Reported Outcomes (PRO): EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L
Data analysis	The primary objective is to evaluate whether capmatinib prolongs PFS by BIRC according to RECIST 1.1 compared to docetaxel. The following null and alternative hypothesis will be tested to address the primary efficacy objective: H_{01}: $\theta_1 \geq 1$ vs. H_{A1}: $\theta_1 < 1$ where θ_1 is the PFS hazard ratio (capmatinib versus docetaxel). The primary efficacy analysis to test these hypotheses and compare the two treatment groups will consist of the stratified log-rank test at an overall one-sided 2.5% significance level. The stratification will be based on the stratification factor assigned at randomization, i.e. the number of prior lines of systemic therapy (one line vs. two lines). The analysis will be performed on the Full Analysis Set. PFS will be summarized using the Kaplan-Meier method. Median PFS, with corresponding 95% CI, and 25^{th} and 75^{th} percentiles will be presented by treatment group. The hazard ratio for PFS will be estimated, along with its 95% confidence interval, using a stratified Cox proportional hazard model using the same stratification factor as for the log-rank test. Refer to Section 2.1 for the definition of the primary estimand and to Sections 12.4.1 to Section 12.4.6 for details on censoring, intercurrent events, as well as sensitivity and supplementary analyses for the primary efficacy endpoint. The analyses for secondary objectives are detailed in Section 12.5.
Key words	Capmatinib, MET, NSCLC, INC280, docetaxel

[redacted]

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 2019, approximately 142,670 deaths due to lung cancer are expected in the United States (US) (Siegel et al 2019) and 280,000 in the European Union (Malvezzi et al 2019).

Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancer cases, and it includes two major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types); and (2) squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most common type accounting 50% of NSCLC and is also the most frequently occurring cell type in non-smokers (Subramanian and Govindan 2007, Perez-Moreno et al 2012, Novello et al 2016).

Mechanisms of oncogenesis in lung cancer have been largely deciphered over the past 20 years. The concept of "oncogene addiction" refers to tumor-cell dependence on the specific activity of an activated or overexpressed oncogene. The main oncogenic drivers in the field of thoracic oncology are mutations of EGFR, and ALK rearrangements. They are most often reported in adenocarcinomas. However, new molecular targets have been highlighted recently: e.g. MET, KRAS, BRAF, HER2, PIK3CA mutations, translocations, such as ROS1 and RET, NTRK fusions, etc. Therapeutic strategies have been designed to inhibit these signaling pathways, among which are monoclonal antibodies and tyrosine-kinase inhibitors (TKIs).

Treatment options for patients with advanced NSCLC with no established and druggable molecular driver (e.g. ALK gene rearrangements, ROS1 rearrangements, sensitizing EGFR mutations and BRAF V600E point mutations) are based on immunotherapy (immuno-oncology [IO]), either as monotherapy or in combination with platinum doublets in the first line setting, as well as monotherapy options for patients who progressed to platinum based chemotherapy (Planchard et al 2018, NCCN Guidelines Version 1, 2022). Alternatively, systemic chemotherapy without the addition of IO is an option for patients not eligible for single agent or combination IO therapy (Scagliotti et al 2014, Malhotra et al 2017). Single agent chemotherapy remains an established treatment option for pre-treated NSCLC patients. Docetaxel monotherapy is approved for all histologic subtypes and has served as a control arm for several prospective, randomized trials in second- or third-line settings (Borghaei et al 2015, Brahmer et al 2015, Herbst et al 2016, Rittmeyer et al 2017). For docetaxel, please refer to Section 4.3 and local prescribing information. Moreover, in some countries also ramucirumab, a VEGF receptor antibody, and nintedanib, an anti-angiogenic multi-TKI, are approved for second and further line treatment in combination with docetaxel.

Upon progression after second-line chemotherapy, patients may be candidates for further treatment, although randomized evidence is scarce and most data come from phase II trials or retrospective analyses. Patients often have limited response to third-line therapy, although it may have some palliative effect (Shepherd et al 2005, de Marinis and Grossi 2008, Eccles et al 2011, Besse et al 2014, Reck et al 2014, Novello et al 2016).

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MET is a receptor tyrosine kinase involved in embryogenesis, organogenesis and tissue damage repair (Birchmeier and Gherardi 1998, Birchmeier et al 2003). MET-pathway dysregulation through receptor overexpression, genomic amplification, mutations, autocrine or paracrine secretion of its ligand (Hepatic Growth Factor–HGF) has been shown to be oncogenic, promoting cell-cell detachment and metastasis, epithelial-mesenchymal transition, invasion, angiogenesis, proliferation and survival (Christensen et al 2005). Awad and colleagues showed that MET mutation is a negative prognostic factor in advanced NSCLC patients (n=61): 40% of the patients included in this retrospective study had brain metastases and median OS (from stage IV diagnosis) was 8.1 months and was shorter (5.2 months) when MET amplification and mutation were concurrent (Awad et al 2019). MET mutations leading to exon 14 deletion (referred to as MET mutation(s) or METΔex14 mutations hereafter) have been identified as an additional actionable target for MET inhibition in NSCLC (Kong-Beltran et al 2006). The loss of exon 14 deletes the region of the protein required for the CblE3 ligase to bind to MET and target it for degradation. This results in extended MET occupancy at the membrane and ultimately activation of the receptor. Based on the epidemiology data currently available, MET mutations can be detected in 2-4% 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, Ou et al 2016, Tong et al 2016). 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, Liu et al 2015, Mendenhall and Goldman 2015, Paik et al 2015, Waqar et al 2015, Drilon 2016, Schuler et al 2016, Awad et al 2019, Wolf et al 2019, Wolf et al 2020, Paik et al 2020).

1.1.1 Overview of capmatinib (INC280)

Capmatinib (INC280) is a small adenosine triphosphate (ATP) competitive, orally bioavailable, highly potent, and selective reversible inhibitor of the MET receptor tyrosine kinase (Liu et al 2011, Baltschukat et al 2019).

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, Baltschukat 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 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

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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 28-Sep-2021, 863 participants with solid tumors have been treated with capmatinib as a single agent, 810 participants have received capmatinib in combination with other therapies and 1246 patients have received capmatinib under Managed Access Program (MAP). The recommended phase II dose (RP2D) for capmatinib as a single agent has been determined to be 400 mg b.i.d. in tablet formulation [capmatinib Investigator's Brochure].

The most frequent AEs suspected to be related to capmatinib of any grade reported in study [CINC280A2201], reference study for the safety profile of capmatinib monotherapy (n=373), across study cohorts and irrespective of MET mutational status, were edema peripheral (46.1%), nausea (34.3%), blood creatinine increased (19.8%), vomiting (19.0%), fatigue (13.7%), decreased appetite (12.6%) and diarrhea (10.7%); the majority were Grade 1/2.

The Grade 3/4 AEs suspected to be related to capmatinib in the [CINC280A2201] study included edema peripheral (8.8%), alanine aminotransferase increased (5.6%), lipase increased (5.6%), amylase increased (3.2%), fatigue (2.7%), aspartate aminotransferase increased (2.4%), vomiting (1.9%), nausea (1.6%), decreased appetite (0.8%), asthenia (0.8%), constipation (0.5%), rash (0.3%) 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 Cohort 4 ($2^{nd}/3^{rd}$ line) and Cohort 6 (2^{nd} line) of phase II GEOMETRY 1 study [CINC280A2201]. As of 18-Sep-2020, the ORR by BIRC (95% CI) was 40.6% (28.9, 53.1) for Cohort 4 (n=69) and 51.6% (33.1, 69.8) for Cohort 6 patients (n=31) using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Evaluable patients were defined as those with at least one post-baseline tumor assessment or have discontinued treatment at the time of the data cut-off. The median DOR (95% CI) by BIRC was 9.72 (5.55, 12.98) months for Cohort 4 patients, and 8.38 months (4.17, NE) months for Cohort 6 patients. The median PFS by BIRC (95% CI) was 5.42 (4.17, 6.97) months for Cohort 4 patients and 6.93 months (4.17, 13.34) for Cohort 6 patients. Median OS (95% CI) was 13.57 months (8.61, 22.24) for Cohort 4 patients and not reached for Cohort 6 patients.

Moreover, in a post-hoc analysis, a promising intracranial activity with capmatinib was observed in patients with brain metastases based on medical review of central neuroradiologic assessment of brain lesions. Of the 28 evaluable patients by BIRC with NSCLC and MET exon 14 skipping mutation who had brain lesions at baseline and at least one post-baseline tumor assessment, 16 subjects showed intracranial lesion shrinkage (9/16 patients had complete disappearance of intracranial lesions) and 25 subjects had an intracranial disease control.

Capmatinib received breakthrough therapy designation for treatment of treatment-naive and pre-treated NSCLC patients with METΔex14 mutations from the US Food and Drug Administration (FDA). FDA also granted an orphan drug designation to capmatinib for treatment of patients with MET dysregulated NSCLC. Subsequently, capmatinib received

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approval in US, Japan, Switzerland and several other countries for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping. A companion diagnostic approval in tumor and plasma was also granted in US and Japan.

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.

Capmatinib may be administered with or without food. 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.

Capmatinib is a moderate cytochrome P450 enzyme 1A2 (CYP1A2) inhibitor [CINC280A2103] and an inhibitor of P-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 coadministration is unavoidable, decrease the dosage of CYP1A2 substrates, P-gp substrates, or BCRP substrates in accordance with the approved prescribing information.

Capmatinib is a moderate inhibitor of multidrug and toxic compound extrusion (MATE). Based on static DDI risk assessment with Cmax,ss,u/Ki =3, capmatinib is likely a MATE inhibitor at therapeutic concentration. Transient serum creatinine increase following capmatinib administration in contrast to no change in serum cystatin C level indirectly suggest that the transient increase of serum creatinine level may result from reversible inhibition of active renal transporters, in this case, likely MATE1 and MATE2K. However, the likely increase in co-administered MATE substrate exposure will not lead to safety concern with the following evidence: Based on *in vitro* data from the Drug Interaction Database (DIDB) (httpsdidb.druginteractionsolutions.org/) from the University of Washington, MATE inhibitors, cimetidine, pyrimethamine, trimethoprim and ondansetron, all have I unbound/Ki >3.2 (range from 3.2 to 6.3), greater than the I/Ki value for capmatinib. Yet, the corresponding exposure (Cmax or AUC) change in MATE substrates (e.g. metformin, lamivudine and varenicline) when co-administered with these MATE inhibitors is unlikely to cause safety concern as identified MATE substrates are not narrow therapeutic index drugs (except topotecan, which will not be a concomitant medication for capmatinib).

When coadministered with the strong CYP3A inhibitor itraconazole, capmatinib AUC increased by approximately 42% without any change in C_{max}. When coadministered with the strong CYP3A inducer rifampicin, capmatinib AUC and C_{max} decreased by 67% and 56%, respectively [CINC280A2102]. Hence, adverse reactions during coadministration 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].

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1.2 Purpose

The rationale for investigating the anti-cancer activity of capmatinib in this study population of advanced MET mutated NSCLC pre-treated with one or two prior lines of systemic therapy is supported by the following:

- These patients represent a high unmet medical need as MET dysregulation is considered a poor prognostic factor (Dimou et al 2014, Guo et al 2014, Landi et al 2017, Awad et al 2019) and to date there are limited treatment options for NSCLC with MET mutation.
- The evidence of efficacy of standard treatments (either chemotherapy or immunotherapy) in this setting is 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 and Paik 2017, Awad et al 2019).
- Capmatinib is highly potent in NSCLC in both *in vitro* and *in vivo* models [capmatinib Investigator's Brochure].
- Clinical data demonstrate that capmatinib monotherapy has anti-tumor activity in EGFR wt NSCLC harboring MET mutation [CINC280A2201].
- Safety data demonstrate that capmatinib is well tolerated by the target population at the RP2D of 400 mg b.i.d. (tablet) [capmatinib Investigator's Brochure].

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
To compare the efficacy of capmatinib versus docetaxel	Progression-free survival (PFS) by BIRC as per RECIST 1.1 See Section 2.1 for Primary Estimand.
Key secondary objective	**Endpoints for Key secondary objective**
To compare the overall response rate (ORR) of capmatinib and docetaxel	ORR calculated per RECIST 1.1 by BIRC. See Section 2.2 for Secondary Estimand.
Secondary objectives	**Endpoints for secondary objectives**
To assess the antitumor activity of capmatinib versus docetaxel	All calculated per RECIST 1.1, both by BIRC and investigator: • Duration of response (DOR) • Time to response (TTR) • Disease control rate (DCR) All calculated per RECIST 1.1, by investigator: • PFS, ORR
To evaluate overall survival (OS) in participants treated with capmatinib versus docetaxel	Overall survival
To evaluate the safety profile of capmatinib versus docetaxel	Incidence of adverse events and serious adverse events, change in vital signs, laboratory results and ECG
To characterize the pharmacokinetics of capmatinib in this study population	Plasma concentrations at specific time points.

[redacted]

Objectives	Endpoints
To assess the effect of capmatinib versus docetaxel 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-LC13, QLQ-C30, EuroQoL-5 Dimension-5 Level/EQ-5D-5L) questionnaires • Time to symptom deterioration for chest pain, cough and dyspnea in the European Organization for Research and Treatment of Cancer (EORTC) QLQ-LC13 as well as global health status/QoLper QLQ-C30 questionnaire
To assess intracranial anti-tumor activity of capmatinib and docetaxel in participants with Central Nervous System (CNS) lesions at baseline by BIRC	Overall intracranial response rate (OIRR), duration of intracranial response (DOIR), time to intracranial response (TTIR), intracranial disease control rate (IDCR) by BIRC as per RANO-BM criteria

[redacted]

2.1 Primary estimands

The primary scientific question of interest is to estimate the treatment effect based on the primary endpoint of PFS for capmatinib compared to the control arm (docetaxel) for the target population regardless of study treatment discontinuation or start of new antineoplastic therapy.

The justification for targeting this treatment effect is that it will help us to understand the treatment effect of capmatinib relative to docetaxel regardless of subsequent antineoplastic therapy and study treatment discontinuation, which resembles realistic clinical practice.

The primary estimand is characterized by the following attributes:

1. Population: adult participants with EGFR wt, ALK rearrangement negative, locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC harboring MET exon 14 skipping mutation. Further details on the population are provided in Section 5.
2. Treatment: randomized treatment capmatinib versus docetaxel with or without any new post-treatment antineoplastic therapy as needed. Further details about the treatment are provided in Section 6.
3. Variable: progression free survival (PFS) defined as the time from the date of randomization to the date of the first documented disease progression based on BIRC as per RECIST 1.1 or date of death due to any cause, whichever occurs first.
4. Intercurrent events:

[redacted]

- Discontinuation of study treatment for any reason before PFS event (radiological progression or death):
  PFS will take into account all PFS events irrespective of the study treatment discontinuation reasons (treatment policy strategy)
- Any unforeseen intercurrent events (e.g., Coronavirus Disease 2019 (COVID-19) pandemic related events):
  PFS will take into account all PFS events irrespective of any unforeseen intercurrent events (treatment policy strategy)

5. Summary measure: PFS hazard ratio (HR) between the two treatment arms (capmatinib versus docetaxel). It will be estimated using a Cox proportional hazard model stratified by the randomization stratification factor. PFS will be tested using the log-rank test stratified by the randomization stratification factor.

2.2 Secondary estimand

The key secondary scientific question of interest is to estimate the treatment effect of capmatinib and compared to the control arm (docetaxel) based on ORR for the target population regardless of discontinuation of treatments and any unforeseen events resulting from a Public Health emergency (e.g. COVID-19). The secondary estimand is defined by the following attributes:

1. Population: adult participants with EGFR wt, ALK rearrangement negative, locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC harboring MET exon 14 skipping mutation. Further details on the population are provided in Section 5.
2. Treatment: randomized treatment capmatinib versus docetaxel.
3. Variable: best overall response (BOR) defined as the best response recorded from the date of randomization until disease progression/recurrence (taking as reference for disease progression the smallest measurements recorded since the treatment started) based on BIRC per RECIST 1.1 with responses after the use of new anti-cancer therapy considered as non-response.
4. Intercurrent events
   - Discontinuation of study treatment for any reason: BOR will take into account all response assessments irrespective of the study treatment discontinuation reasons (treatment policy strategy)
   - Any unforeseen intercurrent events (e.g. related to a Public Health emergency, like the COVID-19 pandemic) will be handled by the treatment policy strategy
5. Summary measure: difference in ORR (defined as the proportion of participants with confirmed BOR of complete response or partial response based on BIRC per RECIST 1.1) of the two treatments and its 95% confidence interval based on the stratified Miettinen-Nurminen method (Miettinen and Nurminen 1985) with randomization strata weighting by sample size with a single treatment covariate.

[redacted]

3 Study design

This is a multicenter, open-label, randomized, active-controlled, global phase III study that will enroll adult participants with EGFR wt, ALK rearrangement negative, NSCLC harboring METΔex14 skipping mutations who have progressed on one or two prior lines of systemic therapy for locally advanced or metastatic stage and are candidates for docetaxel.

The study will randomize approximately 90 participants globally. Participants eligible for the study will be randomized in a 2:1 ratio to one of the two treatment arms: capmatinib (investigational therapy) or docetaxel. Additional participants may be randomized to support the analysis of the second supplementary estimand (refer to Section 12.4.6).

The randomization will be stratified by prior lines of systemic therapy received for advanced/metastatic disease (one line vs. two lines).

Participants randomized to docetaxel treatment will be eligible to crossover to receive capmatinib treatment after blinded independent review committee (BIRC)-confirmed, RECIST 1.1-defined progressive disease (PD) and after meeting the eligibility criteria outlined in Section 6.1.5.2.

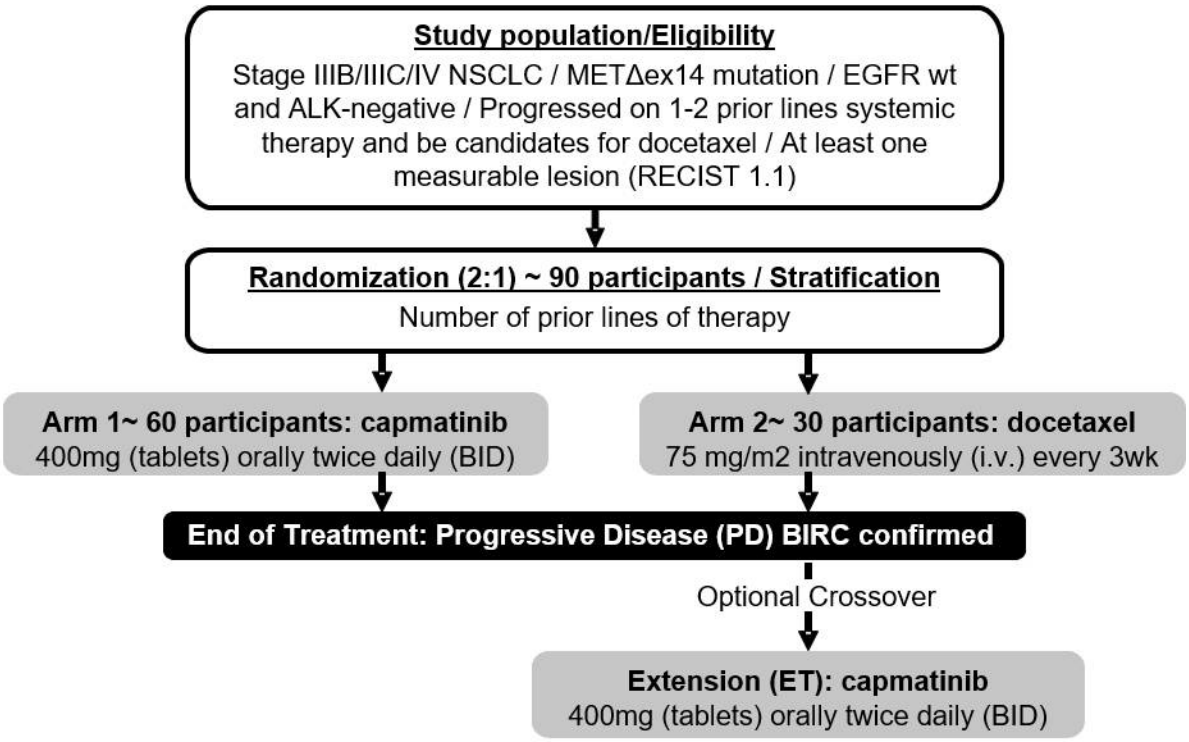
For all participants, the respective treatment (either with capmatinib or docetaxel) may be continued beyond initial disease progression as per RECIST 1.1 (as assessed by the investigator and confirmed by BIRC) if, in the judgment of the investigator, there is evidence of clinical benefit, and the participant wishes to continue on the study treatment (for additional details please refer to Section 6.1.5.1).

After treatment discontinuation, all participants will be followed for safety evaluations during the safety follow-up period. Following completion of all study assessments (as applicable), the participant's status will be collected every 12 weeks as part of the survival follow-up (for additional details please refer to Section 9).

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

[redacted]

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. All participants must sign the molecular pre-screening ICF, regardless of if they have a local METΔex14 mutation positive result or if they will be submitting a tumor sample for central pre-screening by the Novartis-designated laboratory for determination of their METΔex14 mutation status.

Screening and Randomization

Participants must sign the main Informed Consent Form (ICF) prior to any study specific screening evaluations and as early as 28 days prior to the randomization.

Following completion of all required screening procedures (refer to Section 8.2) and verifying participant eligibility, the participant will be randomized via the Interactive Response Technology (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).

[redacted]

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

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

Participants randomized to the docetaxel arm will be allowed to crossover to receive capmatinib therapy after BIRC-confirmed, RECIST 1.1-defined PD. Such participants must complete the EOT visit after permanent discontinuation of docetaxel. The subsequent ET-EOT visit will be performed for participants who crossover from the docetaxel arm to capmatinib when these participants permanently discontinue treatment with capmatinib.

Post-Treatment Follow-Up (Safety, Efficacy and PRO Follow-Up)

After treatment discontinuation, all participants will be followed for safety evaluations during the safety follow-up period as outlined in details in Section 6.5.2 and Section 9.3.1. Participants will be followed for safety up to 30 days after the last dose of study treatment. If a new antineoplastic therapy is initiated after end of 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 BIRC confirmed PD will continue efficacy assessments (Efficacy Follow-up) during the post-treatment follow-up until documented RECIST 1.1-defined PD as assessed by the investigator and confirmed by BIRC, participant withdrawal of consent, lost to follow-up, death or study is terminated by the sponsor as outlined in Section 9. For these participants, patient-reported outcomes will also continue to be collected (Efficacy and PRO Follow-up).

Survival Follow-up

After study treatment discontinuation or post-treatment follow-up phase discontinuation, as applicable, the participant's survival status will be collected every 12 weeks (via phone calls) as part of the survival follow-up phase.

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

4 Rationale

4.1 Rationale for study design

The rationale for the study design is described in Table 4-1.

[redacted]

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Study population	The study will enroll participants with locally advanced/metastatic NSCLC, which are EGFR wt (for EGFR mutations that predict sensitivity to EGFR therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations), ALK negative and harbor METΔex14 mutations, after failure of the first line treatment for the advanced stage. Participants must be docetaxel naive and candidates for single agent chemotherapy (docetaxel) and progressed on or after the last therapy before study entry. Participants with other druggable targetable oncogenic drivers (such as BRAF, ROS1, RET, NTRK, KRAS, etc.) will be excluded. For more details on participant population, please refer to Section 5.
Comparator treatment	Docetaxel was selected as the comparator treatment as it is a globally established standard of care in this pre-treated setting, irrespective of the histology and has been used as a comparator in many phase III studies in a similar setting.
Open-label	The trial is open-label for the following reasons: effective blinding could be difficult given the 1) difference in premedication requirements between the two arms, which would pose also an unnecessary burden for the participants and 2) varying toxicities between the study treatments
Stratification factors	Number of prior lines of therapy was chosen as a stratification factor due the expected difference in clinical outcome between participants based on the number of prior lines of therapy received.
Randomization and 2:1 ratio	Participants will be randomized with a 2:1 ratio, as the efficacy of standard therapies in this setting is currently unknown. Therefore, the randomization 2:1 increases the chances for participants to receive capmatinib, the innovative MET inhibitor, which exhibits meaningful clinical activity.
Treatment beyond disease progression	This is to ensure those participants (in either arm) who have disease progression per RECIST 1.1 as assessed by the investigator and confirmed by BIRC to continue study treatment, as long as they are clinically stable, tolerate the treatment, and are deriving clinical benefit. Timely follow-up after the initial PD will ensure that participants with confirmed/rapid progression will be discontinued and can initiate alternative therapies.
Crossover	The possibility to crossover increases the chances for participants treated with docetaxel to receive the innovative MET inhibitor capmatinib, which has shown meaningful clinical activity in this patient population of METΔex14 NSCLC.

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 has been declared the recommended phase II dose (RP2D) [CINC280X2102]. Furthermore, robust efficacy has been demonstrated in both 2/3L and 1L MET mutant NSCLC patients at this dose level [CINC280A2201]. In addition, sustained target coverage was expected at this dose as 96% of patients 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].

[redacted]

In this study, duration of treatment is continuous until disease progression or other reasons for drug discontinuation. Treatment with capmatinib may be continued beyond RECIST 1.1-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

Docetaxel is a global established treatment option for pre-treated NSCLC patients and has served as a control arm for several prospective, randomized trials in the second- or third-line setting including the most recent phase III studies with PD-1/PD-L1 inhibitors (Borghaei et al 2015, Brahmer et al 2015, Herbst et al 2016, Rittmeyer et al 2017), and it is approved for the use in NSCLC irrespective of tumor histology. The combination of nintendanib or ramucirumab with docetaxel is also one treatment option for fitting patients approved in some countries in the pre-treated NSCLC setting (Janning and Loges 2018). In the context of the post-platinum setting, a response rate of approximately 9-10%, median PFS of 2-4 months, and median OS of approximately 6-9 months is expected with docetaxel (Hanna et al 2004, Borghaei et al 2015, Brahmer et al 2015, Herbst et al 2016, Rittmeyer et al 2017). Overall, the reported response rates to second-line chemotherapy (including other single agent chemotherapeutics) have generally been less than 10%, with median PFS and OS generally below 3 and 8 months, respectively (de Marinis and Grossi 2008, Weiss and Stinchcombe 2013, NCCN 2020). Upon progression after second-line chemotherapy, patients may be candidates for further treatment, although randomized evidence is scarce and most data come from phase II trials or retrospective analyses. Patients often have limited response to third-line therapy, although it may have some palliative effect (Shepherd et al 2005, de Marinis and Grossi 2008, Eccles et al 2011, Besse et al 2014, Reck et al 2014, Novello et al 2016, NCCN 2020). While published data are still lacking, as no sub-analysis for MET dysregulated NSCLC have been conducted, poorer outcome is expected in the target population due to the negative prognostic impact of MET dysregulation (Dimou et al 2014, Guo et al 2014, Landi et al 2017, Awad et al 2019).

We are expecting that the majority of participants enrolled in the study would have adenocarcinoma histology, generally treated with a pemetrexed platinum doublet as first line treatment. For those participants who progress, docetaxel would be considered a preferred option in the second line setting.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

[redacted]

4.5 Risks and benefits

The participants enrolled in this study will have stage IIIB/IIIC or stage IV NSCLC. Given the clinical and molecular characteristics of METΔex14 mutated NSCLC, participants have fewer therapeutic options and the established standard of care has limited benefit in this study population.

Capmatinib is one experimental treatment that has shown an acceptable safety profile and clinical 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. For this reason, randomization ratio and crossover strategy were implemented accordingly to ameliorate patient access to the drug (please refer to Section 4.1).

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 adverse events. 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 central METΔex14 skipping mutation test used for enrollment is investigational and how well the test performs to identify patients who are most likely to benefit from capmatinib or whether the benefits of capmatinib treatment will outweigh any potential serious side effects or risks from the use of the test has not been fully established. However, the test is sufficiently validated for the purposes of selecting participants with a MET Δex14 skipping mutation in their NSCLC tumor sample for enrollment to this study.

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 each compound are discussed in Section 4.5.1 and Section 4.5.2. For further details, refer to the toxicity data provided in the [capmatinib Investigator's Brochure] and in the docetaxel local prescribing information.

As per Section 4.6, in the event of a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, the risk to participants can be mitigated by implementing as appropriate and as permitted by local authorities, the following measures (non-exhaustive list): study treatment shipment to participant's homes, phone calls, virtual contacts, home nursing, remote safety monitoring, remote site monitoring. The impact of a public health emergency on the study data and participant safety will be assessed, if necessary, by collecting protocol deviations and planning additional safety analysis.

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.

[redacted]

Therefore, the overall safety risk to participants enrolled in this study is considered manageable, based on the available clinical safety data for both capmatinib and docetaxel, 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 METΔex14 mutated NSCLC population is consistent with the safety profile of capmatinib across multiple clinical studies. In the context of the significant clinical benefit observed for this study population with limited effective therapeutic options, the overall safety profile is acceptable, and the benefit/risk favorable (see Section 1.2).

The most frequent safety findings 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 changes in liver function test (LFT): 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 could not be 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 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 and Drug-Drug Interaction (DDI), please refer to the current [capmatinib Investigator's Brochure].

4.5.2 Docetaxel

Docetaxel as single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum chemotherapy. In this patient population, its safety and efficacy has been well established since its first approval in 1996. The median survival was 9.0 months with docetaxel versus 4.6 months for best supportive care (BSC) (P = 0.016) (Fossella 2002). Quality-of-life analysis showed significant improvement in several disease-related symptoms in patients who received docetaxel.

The very common adverse reactions to docetaxel are infections, neutropenia, anemia, thrombocytopenia, anorexia, peripheral sensory neuropathy, nausea, stomatitis, vomiting, diarrhea, alopecia, skin reaction, asthenia, fluid retention and pain.

[redacted]

The common adverse reactions to docetaxel are febrile neutropenia, hypersensitivity, peripheral motor neuropathy, arrhythmia, hypotension, constipation, nail disorders, myalgia and blood bilirubin increased.

Tumor lysis syndrome (including fatal outcomes) and myositis have been reported from post-marketing setting with docetaxel (frequency not known).

Docetaxel monotherapy is approved worldwide for the treatment of advanced NSCLC and is recognized as a standard of care.

Please refer to the current local prescribing information for docetaxel in this disease setting.

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 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

This study will enroll adult male and female participants with EGFR wt, ALK rearrangement negative, advanced (stage IIIB, IIIC or IV) NSCLC harboring METΔex14 mutations and who have progressed on one or two prior lines of systemic therapy for advanced/metastatic disease.

The study will randomize approximately 90 participants globally. Participants eligible for the study will be randomized in a 2:1 ratio to one of the two treatment arms: capmatinib (investigational therapy) or docetaxel.

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. Adult ≥ 18 years old at the time of informed consent.
3. Stage IIIB/IIIC (not amenable to surgery, radiation or multi modality therapy) or IV NSCLC (according to Version 8 of the American Joint Committee on Cancer (AJCC) Staging Manual) at the time of study entry.
4. Histologically or cytologically confirmed diagnosis of NSCLC that is:
    - EGFR wt. This should have been assessed as part of the participant's standard of care by a validated test for EGFR mutations as per local guidelines. The EGFR wt status (for EGFR mutations that predict sensitivity to EGFR therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations) must be

[redacted]

documented in the participant source documents before the participant can be consented for pre-screening for MET mutation status. Participants with NSCLC of pure squamous cell histology can enter pre-screening without EGFR mutation testing or result; however, participants with pure squamous cell histology who are known to have EGFR activating mutations will be excluded.

- AND ALK rearrangement negative. This should have been assessed as part of the participant's standard of care by a validated test. 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; if local ALK testing is not available at the time of molecular pre-screening, participant status will be determined centrally by Novartis. Participants with NSCLC of pure squamous cell histology can enter pre-screening without ALK testing or result, however participants with pure squamous cell histology that are known to have ALK rearrangement will be excluded.
- AND has METΔex14 mutation as determined by Novartis-designated central laboratory or by locally performed, tissue-based test, validated according to local regulation, from a Clinical Laboratory Improvement Amendments (CLIA)-certified US laboratory or an accredited local laboratory outside of the US. The positive METΔex14 mutation result as determined per local test must be documented in the participant's source documents and in the CRF prior to entering main screening.

5. Mandatory provision of a formalin-fixed, paraffin embedded tumor tissue sample (archival tumor block or slides, or a newly obtained tumor sample) with quality and quantity sufficient to allow assessment of METΔex14 mutation status (as defined in the study [laboratory manual]). This pertains to all participants, including those who have a METΔex14 mutation result from a local test. Tumor samples must contain at least 10% tumor content.
6. Participants must have progressed on one or two prior lines of systemic therapy for advanced/metastatic disease (stage IIIB/IIIC [not candidates for surgery, radiation or multi-modality therapy] or IV NSCLC), and must be docetaxel naive and candidates for single agent chemotherapy (docetaxel). Treatment failure is defined as documented disease progression or intolerance to treatment, however participants must have progressed on or after the last therapy before study entry. 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. Neo-adjuvant and adjuvant systematic therapies will count as one prior line of treatment if relapse occurred within 12 months from the end of the neoadjuvant or adjuvant systemic therapy.
7. Participants must have recovered from all toxicities related to prior systemic therapies to grade ≤ 1 (CTCAE version 5.0). Participants with any grade of alopecia and vitiligo are allowed to enter the study.
8. At least one measurable lesion as defined by RECIST 1.1. 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.
9. Participants must have adequate organ function including the following laboratory values at the screening visit:
    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L without growth factor support

[redacted]

- Platelets ≥ 100 x 10^9/L
- Hemoglobin (Hgb) ≥ 9 g/dL
- Calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 45 mL/min
- Total bilirubin (TBIL) ≤ ULN (upper limit of normal)
- Aspartate transaminase (AST) ≤ 3 x ULN
- Alanine transaminase (ALT) ≤ 3 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

10. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1.
11. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.
12. Participants must have a life expectancy of at least 3 months.

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 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 on 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 Cycle 1 Day 1.
3. Carcinomatous meningitis.
4. 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: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
5. Participants with known druggable molecular alterations (such as ROS1 and RET rearrangement, BRAF mutation, KRAS mutation, NTRK fusion, etc.) which might be a candidate for alternative targeted therapies.
6. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
7. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome.
8. Clinically significant, uncontrolled heart diseases 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)

[redacted]

- 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
- Fridericia QT correction formula (QTcF) ≥ 470 ms on the screening Electrocardiogram (ECG) (as mean of triplicate ECG)

9. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting Cycle 1 Day 1 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 Cycle 1 Day 1, or participants who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions or radio-surgery for isolated brain lesions ≤ 2 weeks prior to Cycle 1 Day 1 is allowed.
10. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to starting study treatment (2 weeks for resection of brain metastases), or participants who have not recovered from the side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and participants can be enrolled in the study ≥1 week after the procedure.
11. Participants receiving treatment with strong inducers of CYP3A and could not be discontinued ≥ 1 week prior to the start of treatment.
12. Previous anti-cancer and investigational agents within 4 weeks or ≤ 5 x half-life of the agent (whichever is longer) before first dose of study treatment. 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.
13. Impairment of 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 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.

    Active infections include but are not limited to Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV). Screening for known chronic conditions is not required. Participants with known serologic evidence of chronic HBV or HCV infection, whose disease is controlled under antiviral therapy, according to local regulations are eligible.

    Participants with known history of testing positive for human immunodeficiency virus (HIV) infection, and with a history of acquired immunodeficiency syndrome (AIDS)-defining

[redacted]

opportunistic infections in the last 12 months prior to the first dose of study treatment must be excluded. HIV participants at high risk or with history of uncontrolled opportunistic infection must also be excluded. To ensure that effective anti-retroviral treatment (ART) is tolerated and that toxicities are not confused with investigational drug toxicities, trial participants should be on established ART for at least four weeks prior to enrollment, they should have the disease under control and suppressed viral loads defined as per local guideline. HIV participants co-infected with hepatitis virus must also be excluded.

16. Participants with known hypersensitivity to docetaxel or intolerance to docetaxel excipients (as per local prescribing information), polysorbate 80, or to capmatinib and any of the excipients of capmatinib (crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes).
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.

    For female participants treated with capmatinib, highly effective contraception must be used during capmatinib treatment and for 7 days after stopping study treatment.

    For female participants treated with docetaxel, a highly effective contraception must be used during the study. Local prescribing information relating the time limits for such precautions and any additional restrictions will be followed.

    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

[redacted]

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 unless they use a condom during intercourse while taking capmatinib and for 7 days after stopping treatment and should not father a child in this period. For male participants treated with docetaxel, they should not father a child after the last dose of treatment for a period defined as per the local prescribing information. 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, BCG, yellow fever, varicella, TY21a typhoid vaccines and COVID-19 vaccines) within 30 days prior to the first dose of study treatment.

6 Treatment

6.1 Study treatment

For this study, the term "investigational or study drug" refers to Novartis study drug capmatinib.

The comparator drug used in this study is docetaxel. "Study treatment" refers to either capmatinib or docetaxel.

Capmatinib will be labelled and provided to sites by Novartis in compliance with legal requirements for each country. Docetaxel will be procured locally as it is commercially available in each participating country.

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

6.1.1 Investigational and control drugs

The study treatment begins on Cycle 1 Day 1 with the first administration of either capmatinib or docetaxel. Cycle 1 Day 1 should occur on the day of randomization or no later than 3 days after randomization.

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the dosage administration eCRF. Refer to Section 6.7.2 for study treatment prescribing and administration information.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Capmatinib (INC280) 150 mg or 200 mg	Film-coated tablet	Oral use	Open-label participant specific; bottles	Global
Docetaxel (as per local product available)	Concentrate for solution for infusion	Intravenous use	Open-label bulk supply; vials	Local

[redacted]

6.1.2 Additional study treatments

No other treatment beyond investigational drug (capmatinib) and control drug (docetaxel) are included in this trial.

6.1.3 Treatment arms/group

Participants will be randomized to one of the following two treatment arms/groups in a ratio of 2:1 according to the stratification factor.

Each treatment cycle is 21 days for both arms.

- Arm 1: Capmatinib
  - Capmatinib 400 mg (tablets) orally twice daily (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
- Arm 2: Docetaxel (reference chemotherapy)
  - Docetaxel 75 mg/m^2 intravenously (i.v.) following local guidelines as per standard of care and product labels (including steroid premedication)
  - Docetaxel will be administered every 21 days. First infusion day defines Cycle 1 Day 1

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- and docetaxel-associated toxicities and dose modification instructions are provided in Section 6.5.

6.1.5 Treatment duration

Participants will be treated until they experience any of the following: unacceptable toxicity, disease progression per RECIST 1.1 as assessed by the investigator and confirmed by BIRC, and/or treatment is discontinued at the discretion of the investigator or the participant. A complete list of the circumstances requiring study treatment discontinuation is provided in Section 9.

Participants may continue treatment beyond BIRC-confirmed disease progression 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.

Participants in the docetaxel arm will be allowed to crossover to receive capmatinib therapy after BIRC-confirmed, RECIST 1.1-defined PD. Criteria for crossover to capmatinib therapy are described in Section 6.1.5.2.

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.

[redacted]

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 will be permitted to continue study treatment beyond disease progression per RECIST 1.1 as assessed by the investigator and confirmed by BIRC, provided they meet all 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

The reasons for the participant continuing treatment beyond progression will be documented in the eCRF.

Participants who meet the above criteria and continue study treatment beyond initial disease progression per RECIST 1.1 will continue all study procedures as outlined in Section 8. Clinical deterioration or suspicion of further disease progression will require a follow-up imaging assessment to 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.

6.1.5.2 Crossover to capmatinib therapy

Participants randomized to the docetaxel arm will be allowed to crossover to receive capmatinib therapy after BIRC-confirmed, RECIST 1.1-defined PD.

Participants must complete the EOT visit after permanent discontinuation of docetaxel prior to crossing over to capmatinib arm.

For participants who discontinue docetaxel for reasons other than BIRC-confirmed, RECIST 1.1-defined PD (such as treatment intolerance, AEs, etc), safety and efficacy follow up assessments as well as PROs collection must continue to be performed as outlined in Table 8-2, while waiting to confirm crossover eligibility.

Of note, participants in the docetaxel arm who have RECIST 1.1-defined PD as assessed by the investigator and confirmed by BIRC but continue to derive benefit from chemotherapy may continue treatment at the investigator's discretion according to local clinical practice. Participants who meet the criteria outlined in Section 6.1.5.1 and continue study treatment beyond initial disease progression per RECIST 1.1 will continue all study procedures as outlined in Section 8.

[redacted]

Participants in the docetaxel arm who elect to crossover to capmatinib therapy must follow the study assessments as per visit schedule in Table 8-3 in the Extension Treatment (ET) Phase. The following eligibility criteria must be confirmed prior to crossing over to capmatinib arm:

- Participants must have recovered from all toxicities related to docetaxel to grade ≤ 1 (CTCAE version 5.0). Exception to this criterion: participants with any grade of alopecia and vitiligo.
- Participants must not have a history or active medical condition of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e. affecting activities of daily living or requiring therapeutic intervention)
- Participants must crossover to capmatinib treatment within 84 days of BIRC-confirmed, RECIST 1.1-defined PD (imaging date). This window is intended to allow the resolution to at least CTCAE grade 1 of the toxicity related to the prior chemotherapy with docetaxel
- Participants with CNS metastases must be neurologically stable
- Participants must have an ECOG PS of 0-2
- Participants must not be pregnant
- Participants must be compliant with the contraception guidelines outlined in Section 5.2
- Participants must have adequate organ function including the following laboratory values prior to commencing treatment of capmatinib in the ET phase:
  - Calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 45 mL/min
  - Total bilirubin (TBIL) ≤ 1.5 x ULN (upper limit of normal)
  - Aspartate transaminase (AST) ≤ 3 x ULN, except for participants with liver metastases, who may only be included if AST ≤ 5 x ULN
  - Alanine transaminase (ALT) ≤ 3 x ULN, except for participants with liver metastases, who may only be included if ALT ≤ 5 x ULN
  - Asymptomatic serum amylase ≤ Grade 2. Participants with Grade 1 or Grade 2 serum amylase 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
- If the participant has not undergone these specific assessment 7 days prior to commencing treatment of capmatinib in the ET phase, they must complete the following assessments via an unscheduled visit prior to the initiation of capmatinib treatment:
  - ECOG-PS
  - Vital signs
  - Hematology labs
  - Chemistry labs
  - ECG
  - Adverse events
  - Concomitant medications
- Participants must not have started another anti-cancer therapy at the end of the treatment phase.

[redacted]

Participants who crossover from the docetaxel arm to capmatinib will have imaging assessments performed according to local clinical practice and institutional guidelines. The disease progression on capmatinib treatment in ET will be determined based on investigator assessment only. When these participants permanently discontinue treatment with capmatinib, they must complete the ET-EOT visit. All these participants will then be followed for safety until 30 days after the last dose of capmatinib.

6.2 Other treatment(s)

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

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapy deemed necessary for the care of the participant (e.g. such as anti-emetics, anti-diarrhea) is permitted, 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 study treatment and prior antineoplastic treatments), blood transfusions, surgeries and procedures (including physical therapy) administered after the participant signs the main study ICF and up to 30 days after the last dose of study treatment will be recorded on the appropriate eCRF. For participants with brain metastases at baseline, corticosteroid use should be collected on the appropriate eCRF until disease progression (as assessed by the 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 therapies (except radiation as allowed per protocol) other than the study medication should be given to participants.

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

- Oral or topical antibiotics
- Medications to prevent or treat nausea, vomiting or diarrhea
- Growth factors (e.g. G-CSF, 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 stimulant
- Pain medication

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

[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:

- **Strong CYP3A inhibitors:** Coadministrating capmatinib with strong CYP3A inhibitor (itraconazole) increased capmatinib AUC_{inf} by 42%. There was no change in capmatinib C_{max}. Closely monitor participants for adverse reactions during coadministration of capmatinib with strong CYP3A inhibitors.
- **Moderate CYP3A inducers:** 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 $AUC_{0\text{-}12h}$ and 34% decrease in C_{max} 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.
- **CYP1A2 substrates with narrow therapeutic index (NTI):** Capmatinib is a moderate CYP1A2 inhibitor. Coadministration of capmatinib increased sensitive CYP1A2 probe substrate (caffeine) AUC_{inf} by 134%. Avoid coadministration of capmatinib with CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, decrease the CYP1A2 substrate dosage in accordance with the approved prescribing information.
- **P-gp and BCRP substrates:** Coadministration of capmatinib increased P-gp substrate (digoxin) exposure (AUC_{inf} and C_{max} by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUC_{inf} and C_{max} by 108% and 204%, respectively). Avoid coadministration of capmatinib with P gp and BCRP substrates where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, decrease the P-gp or BCRP substrate dosage in accordance with the approved prescribing information.
- **Proton pump inhibitor:** Coadministration of capmatinib with proton pump inhibitor (rabeprazole) decreased capmatinib AUC_{inf} by 25% and C_{max} by 38%. Exercise caution during concomitant use of capmatinib with proton pump inhibitors.
- **H_2-receptor antagonists and antacids:** As an alternative to proton pump inhibitors, an H_2-receptor antagonist or antacid can be taken. Capmatinib should be administered at least 3 hours before or 6 hours after an H_2-receptor antagonist. Capmatinib should be administered at least 2 hours before or 2 hours after an antacid.

Refer to Table 16-11 for a list of the medications that require caution when concomitantly used with capmatinib.

For docetaxel, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.

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 at the investigator's discretion following existing local guidelines. Treatment with

[redacted]

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 Permitted 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 BIRC-confirmed, RECIST 1.1-defined PD, radiotherapy is allowed following the same dose adjustment guidance in case capmatinib is continued beyond PD.

6.2.2 Prohibited medication

Coadministration of capmatinib with strong CYP3A inducer (rifampicin) decreases capmatinib AUC_{inf} by 67% and C_{max} by 56% [CINC280A2102], which may decrease capmatinib anti-tumor activity. Therefore, concurrent use of strong CYP3A inducers are prohibited. Capmatinib prohibited medications are listed in Table 16-12.

For docetaxel, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.

Live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines and 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.

Participants enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies while on treatment.

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

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for molecular pre-screening 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 Center Number (Center 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 informed consent form, the participant is assigned to the next sequential Participant No. available.

[redacted]

A new ICF will need to be signed if the investigator chooses to rescreen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.3.2 Treatment assignment, randomization

Following completion of screening procedures, the investigator or his/her delegate will contact the IRT after confirming that the participant fulfils all the inclusion/exclusion criteria. All eligible participants will be randomized via Interactive Response Technology (IRT) in a 2:1 ratio to one of the following treatment arms:

- Arm 1: capmatinib
- Arm 2: docetaxel

The randomization will be stratified by the number of prior lines of therapy received (one line versus two lines).

The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The study treatment phase begins on Cycle 1 Day 1 with the first administration of capmatinib or docetaxel. Cycle 1 Day 1 should occur on the day of randomization or no later than 3 days after randomization.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

This is an open-label study. Treatment assignment will be open to participants, investigator staff, persons performing the assessments, and the Novartis study team. In order to minimize the potential impact of knowledge of treatment assignment, the randomization list will be kept strictly confidential. No aggregate analyses (efficacy or safety across the study) by treatment arm shall be performed prior to the primary analysis.

[redacted]

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:

Docetaxel

Every attempt should be made to maintain the treatment dosing cycle schedule of every 21 days. For participants who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted per the local approved label in order to keep the participant on treatment. Docetaxel dose reduction will follow the local prescribing information. Participants who discontinue docetaxel due to toxicity will have the option to switch to capmatinib therapy only after BIRC-confirmed, RECIST 1.1-defined PD.

Capmatinib

Dose reductions are allowed for capmatinib and should follow the dose reduction steps described in Table 6-2 and Table 6-3. 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 (IC90, 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 NCI Clinical Toxicity Criteria (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 6-3, 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 6-3. 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 6-3).

[redacted]

If the treatment with capmatinib or docetaxel 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 circumstance, 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 rationale should be captured in the source documents.

Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-3 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 6-3 or Table 6-4, 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 6-2 Dose reduction steps for capmatinib

	Starting dose level 0	Dose level -1	Dose level -2
Capmatinib	400 mg b.i.d.	300 mg b.i.d.	200 mg b.i.d.
Note: dose reduction should be based on the worst toxicity demonstrated at the last dose.			

Table 6-3 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/mm^3; < LLN - 1.5 x 10^9/L)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3; < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3; < 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/mm^3; < 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/mm^3; < LLN - 75 x 10^9/L)	Maintain dose level

Grade 2 (PLT < 75,000 - 50,000/mm^3; < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3; < 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/mm^3; < 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level
Febrile neutropenia (ANC < 1000/mm^3 (< 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 (Hemoglobin [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

[redacted]

	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: [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	Mandatory: Permanently discontinue participant from capmatinib treatment
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

[redacted]

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	
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 study drug, 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 study drug by 1 dose level

[redacted]

	· If fails to resolve to ≤ Grade 1 within 7 days or recur after resumption of study drug at decreased dose, permanently discontinue capmatinib
Grade 3 and Grade 4	Mandatory: Permanently discontinue capmatinib. Treat with IV 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
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 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 capmatinib
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 metastases, or elevation of ALP liver fraction in participants with bone metastases [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 etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator. ** 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).	

These dose changes must be recorded on the appropriate eCRF.

[redacted]

6.5.2 Treatment interruption and treatment discontinuation

If the administration of capmatinib is temporarily interrupted for reasons other than toxicity, 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 6-2 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 and Table 8-3.

Participants who discontinue the study due to a study treatment 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 or docetaxel. 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 6-4 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

[redacted]

TOXICITY	FOLLOW-UP EVALUATION
	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 have 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 hr 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 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 hr 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 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hr 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 hr 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 hr 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 hr 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, 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 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.

[redacted]

TOXICITY	FOLLOW-UP EVALUATION
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 hr, 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).

TOXICITY	FOLLOW-UP EVALUATION
	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 institute 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 IV steroids (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, a high dose

[redacted]

TOXICITY	FOLLOW-UP EVALUATION
	oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hr)[b]. If IV 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 corrected for hemoglobin (DLCO); spirometry; resting oxygen saturation Guideline for significant deterioration in lung function: Decrease in spirometry and/or DLCO of 30% and/or O_2 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), these events should be considered as clinically important 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, GGT, prothrombin time (PT)/ International normalized ratio (INR), alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Evaluate status of liver metastases (new or exacerbation) or vascular occlusion – e.g. using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (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 metastases, or elevation of the liver-specific ALP isoenzyme in participants with bone metastases).

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 6-5 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-5 Clinical and diagnostic assessments for LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, 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, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic congestive heart failure, 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, TSH; cardiovascular 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 an 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 an SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

[redacted]

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Every time the study treatment is to be administered, IRT needs to be accessed (please refer to the IRT manual). The date and time of study treatment administration during the study and any deviations from the protocol treatment schedule will be captured 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.

For treatment with docetaxel: exposure to the study treatment will be based on the number of injections administered.

For treatment with capmatinib: 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 document at each visit. All study treatment dispensed and returned must be recorded in a drug accountability log.

Compliance with the study treatment will be assessed by the Clinical Research Associate (CRA) at each visit using vial counts and information provided by the pharmacist or by the investigator. All study treatment dispensed and returned must be recorded in a drug accountability log.

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study treatment in packaging as described under investigational and control drugs (Section 6.1.1).

Capmatinib

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 system and obtaining the medication number(s). The study medication has a two-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

[redacted]

of study drug directly to a participant's home is generally permitted (if allowed by local or regional health authorities and ethics committees) 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 study drug from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3-month 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 including safety assessments, 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.

Docetaxel

Preparation and dispensation of docetaxel should follow local guidelines as per standard of care and product labels.

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 docetaxel 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 or designated site staff 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. The investigator must provide accountability also for locally sourced materials used for administration (e.g. i.v. bags).

If study treatment is administered at home (e.g. capmatinib), 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, 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.

[redacted]

6.7.1.2 Handling of other treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

Table 6-6 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
Capmatinib (INC280) 200 mg or 150 mg	400 mg tablet, orally (2 x 200 mg or 2 x 150 mg [if dose is reduced to 300 mg b.i.d.] or 1 x 200 mg [if dose is reduced to 200 mg b.i.d.], if applicable)	Twice daily
Docetaxel (as per local product available)	75 mg/m^2 i.v. infusion per product label and local guidelines (as per standard of care)	Once every 21 days

6.7.2.1 Capmatinib

Capmatinib tablets will be administered orally on a continuous twice daily (b.i.d.) dosing schedule, 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. The investigator must instruct the participant to take the study drug exactly as prescribed. All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the dosage administration eCRF.

Participants should take 400 mg of capmatinib tablets twice daily (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 doses should be taken 12 (± 4) hours apart, although a 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.

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 on the day of post-dose PK blood sampling, PK sample collection

[redacted]

is at investigator's discretion. If PK sample collection is done, 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 as a case when the full dose is not taken within 4 hours of the scheduled twice daily dosing. If that occurs, then the dose (or part 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).

6.7.2.2 Docetaxel

Docetaxel will be supplied locally as commercially available and labeled accordingly to comply with legal requirements of each country. Chemotherapy administration (including related steroid pre-medication schemes) should follow local prescribing information.

7 Informed consent procedures

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

If applicable, in cases where the participants' 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.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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 drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

[redacted]

The following informed consents are included in this study:

- Molecular pre-screening consent
- Main study consent, which also includes:
  - 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
  - A subsection that requires a separate signature for the 'Optional Collection of Tumor Biopsy' to allow for collection of on-treatment biopsy from participants on capmatinib treatment
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- Home Nursing consent (if applicable)

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

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information. 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, the 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 prevails 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.).

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

8 Visit schedule and assessments

The assessment schedule in Table 8-2 and Table 8-3 lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The table indicates which assessments produce data to be entered into the database (X) or remain in the source documents only (S). The eCRF will not be used as a source document.

Written informed consent must be obtained before any study specific assessments are performed, including those at molecular pre-screening and screening. 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 treatment administration.

Please refer to Table 8-1 for allowable visits window.

[redacted]

Table 8-1 Allowable window for participant assessments

Visit Name	Window allowed
Screening	-28 days to -1 day from first dose of study treatment
Cycle 1 Day 1	Within 3 days after randomization
Cycle 1 Day 15	±3 days
Day 1 of all subsequent cycles and ET cycles	±3 days
Imaging evaluations	±7 days
PROs assessments	• During the treatment and until progression: within 3 days prior to the visit • For EOT and post progression time points: ±7 days of the visit
EOT and ET-EOT	≤ 7 days after stopping study treatment for EOT
30-Day Safety FUP	+7 days
Survival FUP	±14 days

Laboratory assessments performed as part of the screening evaluations will not be required to be repeated on the first day of dosing (Cycle 1 Day 1) (except hematology/chemistry and serum pregnancy test if not done within 72 hours prior to treatment start) unless deemed clinically necessary by the investigator and/or required as per local institutional policies.

Every effort must be made to follow the schedule of assessments (Table 8-2 and Table 8-3) within the windows outlined in the assessment schedule in Table 8-1 or as close to the designated day/time as possible. 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.

Participants who discontinue from study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the eCRF.

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. Depending on local regulations and operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

[redacted]

Table 8-2 Assessment schedule for capmatinib and docetaxel arms

Period	**Screening**		**Treatment Both capmatinib and docetaxel arms**					**Post Treatment FUP Only if RECIST 1.1-defined PD not confirmed by BIRC at EOT. Both capmatinib and docetaxel arms**			**Survival FUP**
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1**		**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PROs FUP**	**End of Post Treatment FUP**	**Post PD PROs FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**	**-**	**Every 12 weeks**
Informed consent for molecular pre-screening	X										
Collection of PD-L1, EGFR wt and ALK rearrangement negative status	X										
If ALK local testing not available, newly obtained tumor biopsy (preferred) or archival tumor sample for central confirmation of ALK negative rearrangement status	X										
Newly obtained tumor biopsy (preferred) or archival tumor sample for central assessment of METΔ14 mutation status	X										
Information on local testing for METΔ14 mutation status	X										
IRT pre-screening registration	X										
Inclusion / Exclusion criteria	X	X									
IRT eligibility check		S									

[redacted]

Period	**Screening**		**Treatment Both capmatinib and docetaxel arms**					**Post Treatment FUP Only if RECIST 1.1-defined PD not confirmed by BIRC at EOT. Both capmatinib and docetaxel arms**			**Survival FUP**
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1**		**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PROs FUP**	**End of Post Treatment FUP**	**Post PD PROs FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**	**-**	**Every 12 weeks**
IRT registration		X	X		X	X					
Main informed consent		X									
Demography	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]			
IRT randomization			X								
Physical examination, including neurological exams		S	As clinically indicated								
Targeted physical examination			S		S	S					
Performance status (ECOG)		X	X		X	X		X[1]			
Body Height		X									
Body Weight		X	X		X	X					
Vital Signs		X	X	X	X	X					

[redacted]

Period	**Screening**		**Treatment Both capmatinib and docetaxel arms**					**Post Treatment FUP Only if RECIST 1.1-defined PD not confirmed by BIRC at EOT. Both capmatinib and docetaxel arms**			**Survival FUP**
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1**		**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PROs FUP**	**End of Post Treatment FUP**	**Post PD PROs FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**	**-**	**Every 12 weeks**
HIV history (HIV testing where locally required)		S									
Hematology		X	X	X	X	X					
Clinical chemistry		X	X	X	X	X					
Coagulation panel		X	As clinically indicated								
Urinalysis (dipstick)		X	As clinically indicated								
Pregnancy Test (serum)		S (≤72 hr before C1D1)				S					
Pregnancy test (urine)					S						
Tumor evaluation		X			Cycle 3 and then every 6 weeks	EOT scan not required if previous scan was performed ≤28 days		Every 6 weeks			
Electrocardiogram (ECG)		X	X		Cycle 2 and if clinically indicated	X					
Adverse Events		Continuously from signing of main ICF until 30 days after last dose of study treatment									

[redacted]

Period	**Screening**		**Treatment Both capmatinib and docetaxel arms**					**Post Treatment FUP Only if RECIST 1.1-defined PD not confirmed by BIRC at EOT. Both capmatinib and docetaxel arms**			**Survival FUP**
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1**		**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PROs FUP**	**End of Post Treatment FUP**	**Post PD PROs FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**	**-**	**Every 12 weeks**
Serious Adverse Events	Continuously from signing of pre-screening ICF until 30 days after last dose of study treatment. Before signing of main ICF, only SAEs suspected to be related to a study procedure are captured							SAEs related to study treatment			SAEs related to study treatment
Pre-dose PROs (EORTC QLQ-C30, EORTC LC13, EQ-5D-5L) **Collection on tablet**			X		Cycle 3 and then every 6 weeks	X		Every 6 weeks			
Pre-dose PROs (EORTC QLQ-C30, EORTC LC13, EQ-5D-5L) **Collection via interview mode**										At 6, 12 and 18 weeks post-BIRC progression -for all capmatinib participants -only for docetaxel participants if participants not eligible to crossover or recovering from	

[redacted]

Period	**Screening**		**Treatment Both capmatinib and docetaxel arms**					**Post Treatment FUP Only if RECIST 1.1-defined PD not confirmed by BIRC at EOT. Both capmatinib and docetaxel arms**			**Survival FUP**
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1**		**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PROs FUP**	**End of Post Treatment FUP**	**Post PD PROs FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**	**-**	**Every 12 weeks**
										docetaxel toxicities waiting for moving to crossover	
Capmatinib administration			Continuous twice daily dosing [b.i.d.]								
Docetaxel administration			X		Every cycle						
Mandatory Blood sample for assessment of METΔ14 status [redacted]	X		X	X[3]	Cycle 3 and then every 3 cycles[3]	X					
[redacted]											
Mandatory, if medically feasible - Capmatinib arm only Newly obtained tumor biopsy. Archival material may be provided instead at Cycle 1 Day 1			X			X (if EOT=PD)					
Optional – Capmatinib arm only [redacted]	[redacted]										

[redacted]

Period	**Screening**		**Treatment Both capmatinib and docetaxel arms**					**Post Treatment FUP Only if RECIST 1.1-defined PD not confirmed by BIRC at EOT. Both capmatinib and docetaxel arms**			**Survival FUP**
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1**		**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Efficacy and PROs FUP**	**End of Post Treatment FUP**	**Post PD PROs FUP**	**Survival FUP**
Days	**-**	**-28 to -1**	**Day1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**	**-**	**Every 12 weeks**
Food consumption[4] - Capmatinib arm only				X							
PK blood collection - Capmatinib arm only				X	Cycle 3 Day 1						
Antineoplastic therapies (meds, surgery, radiation) since discontinuation of study treatment						X	X	X	X		X
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 metastases at baseline
[2] Steroids collection only
[3] Capmatinib arm participants only
[4] Collect information on whether capmatinib was taken in fasted condition or with food

[redacted]

Table 8-3 Assessment schedule for crossover participants

Period	**Extension Treatment (ET) For docetaxel participants who crossover to capmatinib after BIRC-confirmed, RECIST 1.1-defined PD**					**Survival FUP**
Visit Name	**ET-Cycle 1**		**ET-Cycle 2 and beyond**	**ET-EOT**	**Post-ET 30-Day Safety FUP**	**Survival FUP**
Days	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**Every 12 weeks**
IRT registration	X		X	X		
Prior/concomitant medications	Continuously from 28 days prior to first dose until 30 days after last dose of study treatment					
Physical examination, including neurological exams	As clinically indicated					
Targeted physical examination	S		S	S		
Performance status (ECOG)	X		X	X		
Body Weight	X		X	X		
Vital Signs	X	X	X	X		
Hematology	X	X	X	X		
Clinical chemistry	X	X	X	X		
Coagulation panel	As clinically indicated					
Urinalysis (dipstick)	As clinically indicated					
Pregnancy Test (serum)				S		
Pregnancy test (urine)			S			
Electrocardiogram (ECG)	X		ET-Cycle 2 and if clinically indicated	X		
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 main ICF, only SAEs suspected to be related to a study procedure are captured					SAEs related to study treatment

[redacted]

Period	**Extension Treatment (ET)** **For docetaxel participants who crossover to capmatinib after BIRC-confirmed, RECIST 1.1-defined PD**					**Survival FUP**
Visit Name	**ET-Cycle 1**		**ET-Cycle 2 and beyond**	**ET-EOT**	**Post-ET 30-Day Safety FUP**	**Survival FUP**
Days	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**Every 12 weeks**
Pre-dose PROs (EORTC QLQ-C30, EORTC LC13, EQ-5D-5L) **Collection via interview mode**	At 6, 12 and 18 weeks post-BIRC progression (if not collected during docetaxel post-treatment FUP)					
Capmatinib administration	Continuous twice daily dosing [b.i.d.]					
Mandatory Blood sample for assessment of METΔ14 status and [redacted]	X	X	ET-Cycle 3 and then every 3 cycles	X		
[redacted]						
Mandatory, if medically feasible Newly obtained tumor biopsy. Archival material may be provided instead at Cycle 1 Day 1	X			X (if ET-EOT=PD)		
Optional [redacted]	[redacted]					
Antineoplastic therapies (meds, surgery, radiation) since discontinuation of study treatment				X		X
Disposition				X		
Survival (survival information can be obtained via telephone contact)						X

[redacted]

8.1 Molecular pre-screening

In order to be considered eligible for the study, participants must have written documentation of EGFR wt and ALK rearrangements negative NSCLC (not required for participants with pure squamous cell histology, for additional details see Section 5.1). The results from procedures performed as part of the local standard practices (prior to enrolling in the trial) will satisfy the inclusion criteria.

Additionally, eligible participants must have METΔex14 mutation status determined in their tumor tissue sample by the Novartis-designated central laboratory using a validated real time Reverse Transcription (RT) Polymerase Chain Reaction (PCR) test that detects exon 14-deleted MET mRNA derived from formalin fixed, paraffin-embedded human tissue. The central MET Δex14 mutation test is investigational and is sufficiently validated for the purposes of selecting participants with a MET Δex14 mutation in their NSCLC tumor sample for enrollment to this trial. The central test report must be received to confirm eligibility prior to entering main screening.

In cases where it is medically infeasible for the participant to wait for the central METΔex14 mutation result, a local test result may be acceptable for METΔex14 mutation status. The local test must be validated according to local regulation and detect mutations leading to MET exon 14 deletions (METΔex14) in DNA or RNA extracted from a tumor tissue sample. Results from immunohistochemistry tests are not accepted. Positive METΔ14 mutation status must be documented in the participant's source documents and in the CRF to confirm eligibility prior to entering main screening. In cases where there is insufficient evidence that the MET gene alteration detected from the local test leads MET exon 14 deletion, central testing should be performed to confirm METΔ14 status for eligibility. In addition for eligibility, a tumor tissue sample must be submitted with sufficient quality and quantity (as outlined in the study [laboratory manual]) to allow for retrospective central assessment of METΔex14 mutation status using the RT-PCR assay at a Novartis-designated laboratory. If the retrospective central result is negative for the presence of a METΔex14 mutation, participants will not be excluded from the study.

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 to the Novartis-designated central laboratory.

A newly obtained tumor biopsy (preferred) or archival tumor tissue (block or slides) must be submitted to the Novartis-designated laboratory to test for METΔex14 mutation status for all participants. Archival tumor tissue obtained at the time of diagnosis of NSCLC or any time prior to patient enrolling in the study is acceptable. If more than one archival tissue sample is available, tissue from the most recent biopsy is preferred. The quality/quantity of the tumor sample for METΔex14 testing will be determined at the Novartis-designated central laboratory. Tumor samples must contain at least 10% tumor content and the minimum effective tumor area specified in the study [laboratory manual]. Samples obtained from bone metastases and cytology samples are not acceptable. Additionally, a blood sample (2 x 10 mL) will be collected at the Pre-screening visit for potential development of liquid biopsy *in vitro* diagnostic test(s), such as companion diagnostic(s).

[redacted]

If ALK testing is not available locally, confirmation of ALK-negative rearrangement status at a Novartis-designated central laboratory using a validated ALK test is required to confirm the participant's eligibility. In this case, additional tumor sample slides will be provided (unless a tumor block was submitted) and used for METΔex14 mutation testing as well as ALK rearrangement testing and should be indicated in the appropriate eCRF and requisition forms.

If a tumor block or newly obtained biopsy is provided, the remaining tissue from pre-screen failure samples will be returned to the site. [redacted]

Where the result is required for eligibility, the results from central testing will be communicated to the respective study center by the Novartis-designated central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in a separate [laboratory manual].

METΔex14 mutation (and ALK, if applicable) testing may be performed while participant is still receiving anti-cancer therapy. However, the participant can only be screened for the main study once the participant has discontinued the last prior systemic treatment due to either disease progression or intolerance (Note: participants must have progressed on at least one prior line of systemic therapy; for additional details see Section 5.1).

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 performed as part of the screening evaluations will not be required to be repeated prior to dosing (except hematology/chemistry and serum pregnancy test if not done within 72 hours prior to treatment start) unless deemed clinically necessary by the investigator and/or required as per local institutional policies.

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

[redacted]

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 screened and enrolled is likely to ensure target enrollment, 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, e.g. participants confirmed in IRT in error, will be considered as early terminations. The reason for early termination should be recorded on the appropriate eCRF.

8.2.1 Eligibility screening

When all screening procedures are completed and once the participant's eligibility has been checked and confirmed (i.e., all inclusion/exclusion criteria have been verified), the key eligibility criteria checklist will be completed prior to the first dose of study treatment in the IRT system by the investigator or designee. The eligibility check will be embedded in the IRT system. Allocation to one of the two study arms will also be registered via IRT.

Please refer to Section 6.3.2 for further details on treatment assignment/randomization as well as comply with detailed guidelines in the IRT manual.

8.2.2 Information to be collected on screening failures

Both participants who sign a molecular pre-screening informed consent form but are a molecular pre-screening failure, as well as participants who sign the main informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure and data will be handled in the same manner. The reason for screen failure should be recorded on the appropriate eCRF page.

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

- EGFR and ALK status as per participant's record
- PD-L1 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 and ALK (if local ALK status is not available)
- NSCLC diagnosis and extent of disease
  - Date of diagnosis and stage of NSCLC
  - Site of active disease
  - Characteristics of disease

[redacted]

- 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 serious adverse event (SAE) during the screening phase (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.

The demographic information, informed consent, diagnosis and extent of cancer, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.2 and Section 10.1.3 for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.3 Participant demographics/other baseline characteristics

Data to be collected on participant characteristics at screening include:

- Demography (age, gender, race and ethnicity, or as allowed by local regulations). Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities
- 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), baseline PD-L1 tumor status, prior antineoplastic therapies (medications, radiation, surgeries), and date of progression prior to study entry
- Tumor imaging assessments
- Other assessments to be completed for the purpose of determining eligibility (ECOG PS, complete physical examination, vital signs, hematology, blood chemistry, coagulation studies, urinalysis, HIV testing where locally required [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 Cycle 1 Day 1 (C1D1) pre-dose include:

- Patient Reported Outcomes (PROs)

[redacted]

- 12-Lead ECG

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with the eCRF.

8.4 Efficacy

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 by BIRC according to the Novartis guideline version 1 based on Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria (Section 16.2).

Participants should have at least one documented measurable lesion at study entry as per RECIST 1.1. The imaging assessment collection plan is presented in Table 8-4. The central review of the scans will be carried out in a blinded fashion. Further details of the central review process will be described in the BIRC charter.

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 for treatment decision making.

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. 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.

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.

[redacted]

Table 8-4 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 RECIST 1.1-defined PD as assessed by the investigator and confirmed by BIRC. **At End of Treatment** if not done within 28 days. **Post Treatment Follow-Up:** for participants with EOT reason other than disease progression, withdrawal of consent, lost to follow up, or death will continue collect imaging and follow the same schedule of every 6 weeks (+/- 7 days) thereafter until RECIST 1.1-defined PD as assessed by the investigator and confirmed by BIRC
Pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Only if lesions were documented at baseline or if clinically indicated; follow the same schedule as CT/MRI of chest and abdomen
Brain MRI (with intravenous contrast enhancement)	Mandated	Only if lesions were documented at baseline or if clinically indicated; follow the same schedule as CT/MRI of chest and abdomen.
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 baseline or if clinically indicated; follow the same schedule as CT/MRI of chest and abdomen
Color photography (with scale/ruler)	Mandated for any skin lesions present	Only if lesions were documented at baseline or if clinically indicated; follow the same schedule as CT/MRI of chest and abdomen
CT or MRI of other metastatic sites (e.g. neck)	If other metastatic sites are suspected	Only if lesions were documented at baseline or if clinically indicated; follow the same schedule as CT/MRI of chest and abdomen

8.4.1.1 Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1) as per Table 8-4.

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 randomization cannot be considered baseline images.

If a participant is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not

[redacted]

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.

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-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET), or sodium fluoride (NaF) 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, and 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.

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 PD per RECIST 1.1 (Section 16.1).

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 8-4 should be performed at the time points specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 8-1). Imaging assessments for response evaluation will be performed starting at Cycle 3 every 6 weeks (+/- 7 days) thereafter until RECIST 1.1-defined PD as assessed by the investigator and confirmed by BIRC, death, lost to follow-up, or withdrawal of consent. 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

[redacted]

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.

All study imaging (including any off-schedule study imaging) should be submitted to the designated imaging CRO for quality control and review by BIRC, promptly after acquisition.

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 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 and Table 8-4) until the central review determines disease progression.

For participants who crossed-over from the docetaxel arm to capmatinib arm, the disease progression on capmatinib treatment will be determined based on investigator assessment. Imaging assessment should be performed according to local practice and institutional guidelines. Reason for discontinuation and date of disease progression will be captured in the eCRF.

[redacted]

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 disease progression as assessed by the investigator and confirmed by BIRC, tumor assessments must continue to be performed as outlined in Table 8-2. Please refer to Section 9.3 for additional information.

8.4.2 Appropriateness of efficacy assessments

Tumor assessments every 6 weeks of chemotherapy are consistent with the standard clinical practice. Different guidelines for advanced NSCLC recommend response assessment every 6-12 weeks after first line therapy. In participants with NSCLC previously treated with platinum-based chemotherapy, the median PFS with docetaxel treatment is approximately 3 months or 12 weeks. Conducting tumor evaluations more than 6 weeks apart may expose a participant to an unnecessary treatment if the disease progression event takes place between the infrequent assessments or prevent from early identification of progression lesions and appropriate treatment.

8.4.3 Overall Survival

All participants will enter the survival follow-up period once they complete all study assessments per protocol, as applicable. 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. At this time, the investigator will record any SAEs that may have occurred after discontinuation of study treatment if the investigator suspects a causal relationship to study treatment. Information on the therapies received for NSCLC, if any, after study treatment has been discontinued will be collected.

[redacted]

8.5 Safety

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.

For details on AE collection and reporting, refer to AE Section 10.1.

Table 8-5 Physical Assessments

Assessments	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 adverse event on the appropriate eCRF. **Physical examination** At screening, a complete physical examination will be performed including the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological systems. 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 and Table 8-3, 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 participants with brain metastases 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 and Table 8-3.
Height and weight	Height will be measured at screening. Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-2 and Table 8-3.
Performance status	The performance status will be assessed according to the ECOG Performance Status Scale as specified in Table 8-6 following the schedule given in Table 8-2 and Table 8-3.

The ECOG performance status scale will be used as described in Table 8-6 following the schedule given in Table 8-2 and Table 8-3.

[redacted]

Table 8-6 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

A central laboratory will be used for analysis of all specimens collected, except urinalysis, pregnancy testing and HIV testing (where locally required), which will be performed locally. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the [laboratory manual].

Local laboratory assessments may be performed instead of central laboratory assessments if medically indicated or when the treating physician cannot wait for central laboratory results for decision making. In this particular situation, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

The results of the local laboratory will be recorded in the CRF if the following criteria are met:

- a treatment decision was made based on the local results, or
- there are no concomitant central results available

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.

For assessment of participants' eligibility to the study, only laboratory results from the central laboratory will be used.

Table 8-7 Central clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells, Differential [Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other. Absolute value preferred, %s are acceptable unless indicated otherwise]
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Calcium, Magnesium, Phosphate, Sodium, Potassium, Creatinine, Creatine kinase, Creatinine Clearance, Total Bilirubin, Direct Bilirubin (only if total bilirubin is ≥ grade 2), Blood Urea Nitrogen (BUN) or Urea. Amylase, Lipase, Glucose (fasting) (non-fasting allowed post-baseline). Bicarbonate, Chloride, Uric Acid at screening and thereafter if clinically indicated.
Urinalysis	Local laboratory: Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen). If dipstick is abnormal then perform local laboratory Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells).

[redacted]

Test Category	Test Name
Coagulation	Prothrombin time (PT) or Quick Test (QT), INR
Pregnancy Test	At screening (and/or Cycle 1 Day 1) a serum pregnancy test is to be performed within 72 hr before the first dose (either of capmatinib or docetaxel), while during the study (Day 1 of each cycle) urine pregnancy tests are sufficient. An End of Treatment serum pregnancy test is also required to be performed. 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.
Infection markers	HIV testing (where locally required)

8.5.1.1 Hematology

Hematology tests are to be performed according to the Visit Schedules outlined in Table 8-2 and Table 8-3. For details of the hematology panel refer to Table 8-7. Hematology should be assessed on the actual scheduled day, even if study treatment is being withheld.

Laboratory assessment done ≤ 3 days of first dose of study treatment are permitted to be used as Cycle 1 Day 1 labs and do not need to be repeated.

More frequent hematology testing may also be performed as medically necessary. Additional results from unscheduled hematology lab evaluations should be recorded on the appropriate unscheduled visit eCRF.

8.5.1.2 Clinical chemistry

Clinical chemistry tests are to be performed according to the visit schedule outlined in Table 8-2 and Table 8-3. For details of the biochemistry panel see Table 8-7. Biochemistry should be assessed on the actual scheduled day, even if study treatment is being withheld.

Chemistry lab tests done as part of screening assessments ≤ 3 days prior to the first dose of study treatment do not need to be repeated.

More frequent chemistry testing may also be performed as medically necessary. Additional results from unscheduled chemistry lab evaluations should be recorded on eCRF as unscheduled visit.

8.5.1.3 Urinalysis

Urinalysis Dipstick measurements will be performed as per Table 8-7 and according to the schedule of assessments (Table 8-2). Any significant findings on dipstick will be followed up with microscopic evaluation.

8.5.1.4 Coagulation

Coagulation tests outlined in Table 8-7 will be performed according to the visit schedule outlined in Table 8-2 and Table 8-3, as applicable.

[redacted]

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 triplicate 12 lead ECG recording will be performed at the time points indicated in Table 8-8. 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 adverse events 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 initials (where regulations permit), 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 randomizing the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

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.

For all participants (capmatinib, docetaxel, and crossover arms):

Table 8-8 Local ECG collection plan

Cycle	Day	Time	ECG Type
Screening (not required for crossover arm)		Anytime	12 Lead, triplicate
1	1	Pre-dose	12 Lead, triplicate
2	1	Pre-dose	12 Lead, triplicate
		2 hours post-dose	12 Lead, triplicate
End of Treatment		Anytime	12 Lead, triplicate
Unscheduled		Anytime if clinically indicated	12 Lead, triplicate

[redacted]

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 women of child-bearing potential will have a serum pregnancy test within 72 hours prior to the first dose of study treatment. hCG may also be considered a tumor marker, therefore if hCG levels are detected, another blood sample at least 4 days later must be taken to assess the kinetics of the increase, and a transvaginal ultrasound must be performed to rule out pregnancy.

Urine pregnancy tests will be required to be performed on Day 1 of every cycle beginning with Cycle 2, followed by serum pregnancy test at the end of treatment visit.

Women of child-bearing potential will be instructed to contact the site immediately at any time during the study (on-treatment or during follow-up) should they have a positive pregnancy test. In case of positive urine pregnancy testing, additional testing must be performed to confirm the pregnancy, and, if confirmed, follow the reporting requirements as described in Section 10.1.4. A positive pregnancy test requires immediate discontinuation of study treatment. If a positive pregnancy test is performed in between study visits, the participant must immediately notify the investigator. Male participants must notify the investigator in case their partner is confirmed with positive pregnancy test results 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 participants from visiting 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 of the pregnancy test results. Country specific measures should be put in place to ensure site verifies the accuracy of the reported results.

Local pregnancy test and associated results will not be collected on the eCRF.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, Follicle Stimulating Hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

[redacted]

For both treatment arms, when non-child-bearing potential status is determined during the study, further pregnancy testing will not be continued. For further details on the assessment of fertility, please refer to the study exclusion criteria in Section 5.2.

If local requirements dictate otherwise, local regulations should be followed.

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 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

A PRO is a measurement based on a report that comes from the participant (i.e., 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 administered by self-report or by interview, provided that a trained site staff 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 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) and the EuroQoL 5-level instrument (EQ-5D-5L, tablet version) will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms, treatment-related adverse experience, and global health status. The EORTC QLQ-C30, 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/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 hemoptysis, 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

[redacted]

"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 EQ 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).

PRO data will be collected using an electronic device during treatment and post-treatment follow-up period and administered by interview over phone in the post-progression period. All PRO assessments should be administered in the participant's local language and according to the visit schedule in Table 8-2 and Table 8-3, 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 using an electronic device on Cycle 1 Day 1(or within 3 days prior to this visit), Cycle 3 Day 1 (≤3 days) and then every 6 weeks (≤3 days) until End of Treatment (EOT) visit and then:

- For participants who discontinue treatment (capmatinib or docetaxel) due to BIRC-confirmed, RECIST 1.1-defined PD and enter the safety follow-up period, PROs will be collected at EOT (±7 days) and by telephone interview on paper interviewer scripts at 6, 12 and 18 weeks (±7 days) post-progression.
- For participants who discontinue study treatment (capmatinib or docetaxel) for any reason other than BIRC-confirmed, RECIST 1.1-defined PD and enter the efficacy follow-up period, PROs will be collected on electronic device at the same timepoints as the imaging assessments (every 6 weeks) until RECIST 1.1-defined PD. Following progression, PROs will then be collected within 7 days of the
- reported progression, by telephone interview on paper interviewer scripts at 6, 12 and 18 weeks (±7 days) post-progression.
- For participants who discontinue docetaxel treatment and enter extension treatment, PROs will be collected only at 6, 12 and 18 weeks (±7 days) after BIRC-confirmed, RECIST 1.1-defined PD on docetaxel treatmentby telephone interview or by face to face interview in the event participant is at site to perform other assessments. There won't be any possibility to collect data on electronic device.

All PRO questionnaires will also be accessible during unscheduled visits and can be completed at investigator/site team discretion.

[redacted]

The participant must be given the PRO measure(s) to be completed at the scheduled visit before any clinical assessments are conducted. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

Participant questionnaires should be completed in the language most familiar to the participant.

The participant should be given sufficient space and time to complete the PRO measure(s).

The site personnel should check PRO measure(s) for completeness and ask the participant to complete any missing responses. The responses stored electronically in the database will be considered the source file.

The participant should be made aware that completed measure(s) are not reviewed by the investigator/ study personnel.

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, Clinical Outcome Assessments data may be collected remotely (through interviews via phone) depending on local regulations, technical capabilities, and following any applicable training in the required process.

8.6.2 Pharmacokinetics

Serial blood samples will be collected from all participants who receive capmatinib treatment to assess steady-state plasma PK of capmatinib. Time points of blood sample collection for sparse PK analysis are outlined in Table 8-9.

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).

An additional unscheduled PK blood sample will be collected if a participant experiences an AE suspected to be related to study treatment that results in an unscheduled visit or fits the criteria of an SAE (unless participant has interrupted capmatinib for 7 days or more).

[redacted]

Table 8-9 Pharmacokinetic blood collection log for capmatinib

Dose ID following trough PK sampling	Dose ID prior to trough PK sampling	Sample number	Cycle	Day	Scheduled time (hours)	Description
1	101 [a]	11	1	15	0 hr [b]	Pre-dose
1	-	12	1	15	0.5-1.5 hr	Post-dose
1	-	13	1	15	3-5 hr	Post-dose
2	102 [a]	21	3	1	0 hr [b]	Pre-dose
	-	1001 + [c]	NA	NA	Unscheduled [c]	Unspecified

[redacted]

Dose ID following trough PK sampling	Dose ID prior to trough PK sampling	Sample number	Cycle	Day	Scheduled time (hours)	Description
[a] Dose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample [b] PK samples should be taken immediately prior to the next administration of capmatinib. [c] Sample numbers for any unscheduled blood collection for capmatinib will be labeled sequentially starting with 1001.						

8.6.2.1 Pharmacokinetic blood collection and handling

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. At specified time points described in Table 8-9, 3 mL blood draws will be collected into tubes containing K2 EDTA and gently inverted several times to thoroughly mix the anticoagulant. Tubes will be centrifuged to separate plasma and plasma will immediately be transferred into labelled 2 mL polypropylene screw-cap tubes. Plasma samples will be placed in a freezer in an upright position until shipment to the bioanalytical laboratory for analysis.

All sampling is relative to the ingestion of capmatinib. On days and time points where blood PK samples are to be drawn, the PK sample must be drawn first. The exact date and time of dosing, as well as the date and actual time of blood sampling must be recorded on the appropriate eCRF.

If vomiting occurs within 4 hours following capmatinib administration on Cycle 1 Day 1, PK sample collection is at investigator's discretion. If PK sample collection is done, the clock time of vomiting should be recorded in the dosage administration PK eCRF page.

Refer to the [laboratory manual] for detailed instructions for the collection, handling, and shipment of PK samples.

8.6.2.2 Analytical method

Plasma concentrations of capmatinib will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of 1.0 ng/mL by Novartis Bioanalytics. Concentrations below the LLOQ will be reported as 0.00 ng/mL and missing samples will be labelled accordingly.

8.6.3 Biomarkers

Biomarker analyses will be used to investigate the effect of capmatinib in the non-small cell lung cancer patients within the study and in lung cancer in general. [redacted]

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of Novartis. [redacted] Samples and data may be [redacted]

also used to support potential development of *in vitro* diagnostic test(s), such as companion diagnostic test(s).

The sample collection information must be entered on the appropriate sample collection eCRF page(s) and requisition form(s). Detailed instructions for the collection, processing, and shipment of biomarker samples are outlined in the [laboratory manual] for the study. Sample(s) should be collected at the visit/time point(s) defined in Table 8-2, Table 8-3 and Table 8-10.

8.6.3.1 Biomarkers 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 METΔex14 mutation and for ALK rearrangement status, if ALK local testing is not available (Section 8.1). A formalin-fixed, paraffin embedded tumor tissue sample (archival tumor block or slides, or a newly obtained tumor sample) must be provided with sufficient quality and quantity to allow the central assessment of MET mutation status for all participants and for potential development of *in vitro* diagnostic test(s), such as companion diagnostic test(s). [redacted] umor samples must contain at least 10% tumor content and a minimum effective tumor area per slide as described in the study [laboratory manual] and as required for the central assessment of MET mutation status. Samples obtained from bone metastases and cytology samples are not acceptable.

[redacted] For participants randomized to the capmatinib arm or who elect to crossover to capmatinib treatment during the ET Phase of the study, newly acquired core or excisional, formalin-fixed biopsies should be collected at End of Treatment (at first PD if participant continues on treatment post progression and prior to the initiation of any new anticancer therapies), if medically feasible.

[redacted]

[redacted]

8.6.3.2 Biomarker assessments in blood

Blood samples will be collected from all participants at pre-screening, C1D1 (pre-dose) and at EOT. For participants randomized to the capmatinib arm or who elect to crossover to capmatinib treatment during the ET Phase of the study, blood will also be collected at C1D15, C3D1, every third subsequent cycle. Two 10 mL blood samples will be collected ~~£~~. The blood sample collected at pre-screening may be used for development of a potential *in vitro* diagnostic test, such as a companion diagnostic test. [redacted]

Table 8-10 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
Tumor samples			
Mandatory for eligibility for central METΔex14 mutation testing Either newly obtained formalin-fixed biopsy (preferred) or archival tumor block or slides from a formalin fixed paraffin embedded (FFPE) archival biopsy at time of diagnosis of NSCLC or any time since.	Block or a minimum of 13 slides with at least 10% tumor content and a minimum effective tumor area per slide as described in the study [laboratory manual]	Pre-Screening Requires participant's written consent on the molecular pre-screening ICF.	Prior to main screening (if participant has local METΔex14 mutation testing results available, tumor sample should be received before randomization)
Mandatory for eligibility, if ALK local testing is not available. Either newly obtained formalin-fixed biopsy (preferred) or archival tumor block or slides	Block or a minimum of 2 slides	Pre-Screening Requires participant's written consent on the molecular pre-screening ICF.	Prior to main screening

[redacted]

Sample Type	Volume	Visit	Time point
from a formalin fixed paraffin embedded (FFPE) archival biopsy at time of diagnosis of NSCLC or any time since. Material for this test will be taken preferably from the same tumor sample submitted for METΔex14 mutation testing.			
Mandatory for capmatinib or ET-capmatinib participants only, if medically feasible Newly obtained tumor biopsy (preferred), archival material is also acceptable. If a newly obtained tumor biopsy was submitted for molecular pre-screening, this biopsy is not required.	Newly acquired Biopsy or archival material, block (minimum 6-10 slides)	Cycle 1 Day 1	Pre-dose
Optional for capmatinib or ET-capmatinib participants only [redacted]	[redacted]		
Mandatory for capmatinib or ET-capmatinib participants only, if medically feasible Newly obtained tumor biopsy	Newly acquired biopsy (minimum 6-10 slides)	End of treatment	EOT (if EOT=PD) or at 1st PD, if participant continues treatment post progression)
Blood samples			
[redacted]			

[redacted]

Sample Type	Volume	Visit	Time point
[redacted]			

[redacted]

8.6.3.4 Use of residual biological samples

Optional additional biomarker studies

If the participant agrees, the biological samples that remain after analysis is completed (tumor, blood, plasma, and serum) may be kept for up to 15 years to be used for additional studies related to capmatinib or cancer, including research to help develop ways to detect, monitor or treat cancer. [redacted]

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of 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 assessed by the 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 8-1 or Table 8-2, as applicable, and will complete the EOT visit only after permanent discontinuation of study treatment (see Section 6.1.4)

[redacted]

- Adverse event requiring permanent discontinuation of study treatment (see Table 6-3)
- 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 (refer to Section 8).

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.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

For participants who discontinue from study treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, tumor assessments must continue to be performed every 6 weeks until documented disease progression per RECIST 1.1 as assessed by the investigator and confirmed by BIRC, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples.

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 Discontinuation from 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

[redacted]

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/Opposition to use data/biological samples

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. 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.

[redacted]

9.3 Study completion and post-study treatment

For individual participant

Study completion is defined when participant completes all post-treatment follow-up (including 30-day safety follow-up and/or efficacy follow-up 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 approximately 80% 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 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 after the last dose of study treatment. 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 study treatment 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 eCRFs during this follow-up period.

[redacted]

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 study treatment for reasons other than disease progression as per RECIST 1.1 as assessed by the investigator and confirmed by BIRC, death, withdrawal of consent or lost to follow-up will continue to have tumor assessments and PROs collection as per their current schedule until disease progression is confirmed by BIRC, death, withdrawal of consent, lost to follow-up or study terminated by the Sponsor.

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/or efficacy follow-up (if applicable) after treatment discontinuation (whichever is longer) and the post-progression PRO follow-up. 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. At this time, the investigator will record any SAEs that may have occurred after discontinuation of study treatment if the investigator suspects a causal relationship to study treatment.

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 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 sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

[redacted]

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (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 adverse events.

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

For participants 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 adverse events.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events 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.

Adverse events 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).

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

   If CTCAE grading does not exist for an adverse event, 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

[redacted]

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 adverse events 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 CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF 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.

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

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

Once an adverse event 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 1.1 criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to study treatment.

Adverse events 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 drug.

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 adverse events 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

[redacted]

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 adverse event [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
- 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.

All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.

[redacted]

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 serious adverse event 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 Patient Safety Department 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 randomized): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.
- Randomized Participants: SAEs suspected to be causally related to a study procedure are captured between time participant signs molecular pre-screening ICF and signs main ICF. All SAEs collected between time participant signs 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 CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same 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 EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Collection of SAEs 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

[redacted]

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 pre-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 at 1, 3 (for a live birth only) and 12 (for a live birth only) months after the estimated date of delivery 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.

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 (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

[redacted]

within 24 hours of investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

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 a 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 the 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 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 eCRF) 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.

[redacted]

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 adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and 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 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis 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.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the

participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The primary efficacy and safety analyses will be performed after observing approximately 62 PFS events as assessed by BIRC.

Data from participating centers in this protocol will be combined, so that an adequate number of participants will be available for analysis. Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, and efficacy, safety and pharmacokinetic measurements.

Study data will be analyzed and reported in a primary clinical study report (CSR) based on all participants' data up to the time of the data cut-off date determined for the primary efficacy analysis. Any additional data for participants continuing to receive study treatment past the data cut-off date for the primary CSR, as allowed by the protocol, or continuing in the follow-up parts will be reported at completion of the study in a final CSR.

All summaries, listings, figures and analyses will be performed by treatment arms (unless otherwise specified).

Screen failure participants, as described in Section 8.2.2, and the reasons for not being randomized will be reported in a listing, but will not be included in any analyses.

Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP).

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

12.1 Analysis sets

A participant is considered to be enrolled into the study if they have signed the main study informed consent. Only participants who have signed main study informed consent will be included in the analysis data sets.

12.1.1 Full analysis set

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization, regardless of whether or not the treatment was administered. According to the intent to treat principle, participants will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

[redacted]

12.1.2 Full analysis set – brain metastases

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 (SS) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

12.1.4 Pharmacokinetic analysis set

The Pharmacokinetic Analysis Set (PAS) includes all participants who received at least one dose of capmatinib and had at least one steady state evaluable post-baseline capmatinib concentration measurement.

The definition of an evaluable PK concentration profile will be specified in the SAP.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment arm 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.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class, preferred term, and by treatment arm.

12.3 Treatments

The Safety Set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented.

The duration of exposure in weeks to capmatinib and docetaxel as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

The number of participants with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment arm, and all dosing data will be listed.

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

[redacted]

12.4 Primary endpoint(s)/estimand(s) analysis

The primary objective is to evaluate whether capmatinib prolongs PFS by BIRC according to RECIST 1.1 (see Section 16.1) compared to docetaxel. The analysis will be performed on the FAS.

12.4.1 Definition of primary endpoint(s)

PFS is defined as the time from the date of randomization to the date of the first documented progression according to RECIST 1.1, or death due to any cause (see Section 2.1 for further details). In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date (see RECIST 1.1 in Section 16.1 for further details). Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. PFS will be assessed by BIRC according to RECIST 1.1. Censoring conventions (i.e. handling of missing values, censoring, and discontinuations) are provided in Section 12.4.3.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy analysis to test these hypotheses and compare the two treatment groups will consist of the stratified log-rank test at an overall one-sided 2.5% significance level. The following null and alternative hypothesis will be tested to address the primary efficacy objective for PFS based on BIRC as per RECIST 1.1:

$H_{01}: \theta_1 \geq 1$ vs. $H_{A1}: \theta_1 < 1$

where θ_1 is the PFS hazard ratio (capmatinib versus docetaxel). The stratification will be based on the stratification factor assigned at randomization, i.e. the number of prior lines of systemic therapy. If there are too few participants/events in one stratum, an unstratified analysis might be performed. Further details will be provided in the SAP.

The PFS will be analyzed at the primary analysis. PFS will be summarized using the Kaplan-Meier (KM) method, based on the FAS. Median PFS, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented by treatment group. KM estimates for PFS proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided. The hazard ratio for PFS will be estimated, along with its 95% confidence interval, using a stratified Cox proportional hazard model using the same stratification factor as for the log-rank test.

12.4.3 Handling of intercurrent events of primary estimand

The primary estimand will account for the different intercurrent events as follows:

Discontinuation of study treatment for any reason before a PFS event (radiological progression or death): PFS will take into account all PFS events irrespective of the study treatment discontinuation reasons (treatment policy strategy).

New anti-cancer therapy before a PFS event: PFS will take into account all PFS events irrespective of the start of new anti-cancer therapy (treatment policy strategy).

[redacted]

Any unforeseen intercurrent events (e.g., resulting from a public health emergency, like the COVID-19 pandemic): PFS will take into account all PFS events irrespective of any unforeseen intercurrent events (treatment policy strategy).

12.4.4 Handling of missing values not related to intercurrent events

In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date.

Radiological progression or death observed after 2 or more missing tumor assessments will not be included in the derivation of the time to event for PFS, and the observation will be censored at the time of the last adequate tumor assessment prior to the first missing assessment.

Participants without a post-baseline tumor assessment (and without death) will be censored at the time of randomization.

12.4.5 Sensitivity analyses

As a sensitivity analysis, PFS as per local review will be analyzed using a stratified Cox model, with the same analysis conventions as for the primary efficacy analysis. The treatment effect will be summarized by the hazard ratio with its 95% confidence interval. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group.

The number of participants censored and reasons for censoring will be summarized by treatment group using descriptive statistics, presented separately for local review and blinded independent central review.

12.4.6 Supplementary analysis

As supplementary analyses performed in the FAS, the hazard ratio and 95% confidence interval for PFS per BIRC review will be obtained from:

1. An unstratified and covariate-unadjusted Cox model.
2. A stratified and covariate-adjusted Cox model including as potential covariates the following: age, gender, ECOG PS (0, 1), smoking status (smoker, non-smokers, ex-smokers), race (Asian, other). The final covariates will be pre-specified in the SAP.
3. If the primary analysis of PFS is statistically significant, sub group analyses to assess the homogeneity of the treatment effect across demographics and baseline characteristics will be performed. The following subgroups may be considered: gender, age groups (<65, ≥65 years), ECOG PS (0, 1), histology (squamous, non-squamous), smoking status (smoker, non-smokers, ex-smokers), race (Asian, other), and presence or absence of brain metastases at baseline (as assessed by the investigator per RECIST 1.1). A final list of subgroups of interest will be defined in the SAP.

A supplementary estimand will be analyzed with the same target population, primary variable, intercurrent events and summary measure as for the primary estimand. The treatment of interest is the randomized treatment (capmatinib or docetaxel without any antineoplastic therapy post randomization). An additional intercurrent event of antineoplastic therapy post randomization prior to PFS event will be included and handled using the hypothetical estimand strategy i.e.,

[redacted]

PFS will be censored at the date of the last adequate tumor assessment prior to the start of new anticancer therapy if no PFS event is observed prior to the start of new antineoplastic therapy.

A further supplementary estimand will be analyzed with the same treatment of interest, primary variable, intercurrent events and summary measure as for the primary estimand. The target population is the subset of participants for whom the METΔex14 mutation was confirmed by the Novartis-designated central laboratory. A subset of the FAS will be used for this analysis.

12.5 Secondary endpoint(s)/estimand(s) analysis

12.5.1 Efficacy endpoints

The key secondary estimand is defined in Section 2.2 for the key secondary endpoint of ORR. Other secondary efficacy endpoints are the following:

- ORR by investigator assessment as per RECIST 1.1
- DOR, time to response (TTR), and disease control rate (DCR), by investigator assessment and BIRC as per RECIST 1.1
- PFS by investigator assessment as per RECIST 1.1
- Overall Survival
- Overall intracranial response rate (OIRR), duration of intracranial response (DOIR), time to intracranial response (TTIR), and intracranial disease control rate (IDCR) by BIRC as per RANO-BM criteria

12.5.1.1 Key secondary estimand/endpoint

The secondary estimand for ORR is defined in Section 2.2. ORR is defined as the proportion of participants with confirmed best overall response of complete response (CR) or partial response (PR), and will be assessed by BIRC review and according to RECIST 1.1. The following null and alternative hypothesis will be tested using the stratified Miettinen-Nurminen method (Miettinen and Nurminen 1985) to address the key secondary efficacy objective:

$H_{01}: \theta_1 - \theta_2 \leq 30\%$ vs. $H_{A1}: \theta_1 - \theta_2 > 30\%$,

where θ_1, θ_2 are the ORR for the treatment (capmatinib) and control (docetaxel) arms, respectively. ORR will be calculated based on the data from the FAS and strata assigned at randomization. The stratification will be based on the stratification factor assigned at randomization, i.e. the number of prior lines of systemic therapy. A hierarchical testing procedure will be adopted and the testing of the ORR difference will be performed only if the primary endpoint PFS is statistically significant.

If there are too few participants/responders in one stratum, an unstratified analysis might be performed. In case the primary endpoint analysis is not statistically significant, the ORR will be calculated and presented for each treatment group. Further details will be provided in the SAP.

The difference in ORR and its 95% confidence interval based on the stratified Miettinen-Nurminen method with strata weighting by sample size with a single treatment covariate will be reported.

[redacted]

As a supportive analysis, ORR per local investigator assessment will be analyzed using the same method as for ORR by BIRC.

A further supportive analysis will be the ORR by BIRC based on the subset of participants for whom the METΔex14 mutation was confirmed by the Novartis-designated central laboratory.

Further details will be provided in the SAP.

The intercurrent events for the key secondary estimand and handling strategy are described in Section 2.2. The handling of the intercurrent events will allow the inclusion of all BOR in the analysis and is targeting the treatment effect based on ORR due to any cause for capmatinib compared to docetaxel for the target population irrespective of study treatment discontinuation and any unforeseen intercurrent events due to a public health emergency (e.g. COVID-19 pandemic-related events).

The BOR assessments after the use of new anti-cancer therapy will be considered as non-responses and have been accounted for in the variable attribute using the composite strategy.

12.5.1.2 Other secondary endpoints

Duration of response (DOR)

DOR only applies to participants whose BOR is CR or PR according to RECIST 1.1 based on tumor response data. DOR is defined as the time from the date of first documented response (CR or PR) to the first documented progression per RECIST 1.1 or death due to any cause. If a participant with a CR or PR 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. DOR will be assessed by local review as well as by BIRC.

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

Participants continuing without progression or death due to any cause will be censored at the date of their last adequate tumor assessment.

Time to response (TTR)

TTR is defined as the time from the date of randomization to the first documented response of either CR or PR, which must be subsequently confirmed (date of initial response is used, not date of confirmation), according to RECIST 1.1 (see Section 16.1). TTR will be presented by local assessment as well as BIRC assessment.

All participants in the FAS will be included in TTR calculations. Participants without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e. LPLV−FPFV) for participants with a PFS event, or at the date of the last adequate tumor assessment for participants without a PFS event. TTR will be summarized using the Kaplan-Meier (KM) method, based on data from the FAS. Median TTR, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be

presented. KM estimates for TTR proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

Disease control rate (DCR)

DCR is defined as the proportion of participants with a BOR of confirmed CR, PR and stable disease (SD) according to RECIST 1.1 (see Section 16.1). DCR will be assessed by local review as well as by BIRC.

DCR will be calculated based on the data from the FAS and the corresponding 95% confidence intervals based on the exact binomial distribution (Clopper and Pearson 1934) will be presented.

Progression-free survival (PFS)

The analysis in this section refers to the PFS as per local investigator review.

PFS is defined as the time from the date of randomization 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 time points, 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 the date of randomization to the date of death due to any cause. If a participant is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cut-off date. OS will be summarized using the KM method, based on data from the FAS. Median OS with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for OS proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

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.

[redacted]

Duration of intracranial response (DOIR)

DOIR only applies to participants whose confirmed 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 the first documented intracranial progression per RANO-BM criteria as assessed by BIRC review or the 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.

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 time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

Time to intracranial response (TTIR)

TTIR is defined as the time from the date of randomization 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 a 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 a PFS event.

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

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.

12.5.2 Safety endpoints

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

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post

[redacted]

treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

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

1. Pre-treatment period: from date of participant's first informed consent to the date before first administration of study treatment.
2. On-treatment period: from date of first administration of study treatment to the earlier of
   - 30 days after date of last administration of study treatment (including start and stop date),
   - the date prior to start of ET with capmatinib following crossover from docetaxel.
3. Post-treatment period: starting at day 31 after last administration of study treatment or the first day of ET with capmatinib.

Further details will be included in the SAP.

Adverse events

The number (and percentage) of participants with treatment-emergent adverse events (events started after the first administration of study treatment or events present prior to start of study treatment but increased in severity based on preferred term) 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.

Separate summaries will be provided for study treatment related adverse events, deaths, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment. A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

The number (and proportion) of participants with adverse events of special interest will be summarized.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

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

All AEs, deaths, and serious adverse events (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.

Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters will be collected: systolic and diastolic blood pressure (mmHg), pulse (beats per minute), body temperature (°C), weight (kg), and height (cm).

All vital signs data will be summarized by treatment arm and visit/time. The number and percentage of participants with notable vital sign values will be presented for the safety set. A

[redacted]

listing of participants with notable vital signs will be provided and values measured after the on-treatment period will be flagged in the listing. Notable criteria for vital sign values will be specified in the SAP.

12-lead ECG

12-lead ECGs including PR, QRS, QT and QTcF intervals and heart rate will be obtained for each participant during the study. ECG data will be read and interpreted centrally. The average of the ECG parameters at each assessment should be used in the analyses. ECGs collected during the on-treatment period will be summarized. The number and percentage of participants with notable ECG values will be presented for the safety set. A listing of participants with notable ECGs will be provided and values measured after the on-treatment period will be flagged in the listing. Notable ECG value criteria will be specified in the SAP.

Clinical laboratory evaluations

All laboratory data will be summarized by treatment arm and visit/time.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 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 version 5.0, results will be categorized as low/normal/high) based on laboratory normal ranges.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 5.0 grades, if applicable, and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE version 5.0:

- 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 version 5.0 grades to compare baseline to the worst on-treatment post-baseline value.

For laboratory tests where grades are not defined by CTCAE version 5.0:

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

In addition to the above mentioned tables and listings, [redacted] be specified in the SAP.

12.5.3 Pharmacokinetics

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

[redacted]

Capmatinib plasma concentration data will be listed by participant and visit/sampling time point. Descriptive summary statistics will be provided for capmatinib pre-dose (trough) concentrations by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Descriptive summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics. Zero concentrations will not be included in the geometric mean calculation and the CV.

If there are sufficient data for analysis, the details of the population pharmacokinetic analyses will be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report. Data from this and other studies may be pooled for analysis.

12.5.3.1 Handling of missing values/censoring/discontinuations

Missing values for any PK concentrations will not be imputed and will be treated as missing. Below the limit of quantitation (BLQ) values will be set to zero by the bioanalyst and will be displayed in the listings as zero and flagged. BLQ values will be treated as missing for the calculation of the geometric means and geometric CV%.

12.5.4 Patient reported outcomes

Three patient-reported outcomes questionnaires will be assessed: EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L. Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide for each respective patient questionnaire (Fayers 2001, Van Reenen et al 2019). Details will be provided in the SAP.

Descriptive statistics will be used to summarize the scored scales and subscales of the EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L at each scheduled assessment time point for each treatment group. Additionally, change from baseline in the scale and subscale values at the time of each assessment will be summarized. Participants with an evaluable baseline score and at least one evaluable post-baseline score during the treatment period will be included in the change from baseline analyses.

The distribution of time to symptom deterioration will be analyzed by treatment group for chest pain, cough and dyspnea scores per QLQ-LC13 as well as global health status/QoL per QLQ-C30 questionnaire. It will be estimated using the Kaplan-Meier method and the median time along with two-sided 95% CIs will be presented. The hazard ratio will be estimated, along with its 95% confidence interval, using a stratified Cox proportional hazard model using the randomization stratification factor. Further details will be specified in the SAP.

The number of participants completing each questionnaire and the number of missing or incomplete assessments will be summarized by treatment group for each scheduled assessment time point. No formal statistical tests will be performed for PRO data and hence no multiplicity adjustment will be applied. The FAS will be used for analyzing PRO data.

[redacted]

Additional analyses may be performed if deemed necessary. Such analyses will be defined in the SAP.

12.6 Analysis of exploratory endpoints

Analysis of exploratory endpoints will be detailed in the SAP.

12.7 Interim analyses

No formal interim analysis is planned for this trial.

The primary analysis will be performed after approximately 62 PFS BIRC assessed events have been documented. Formal testing of the primary endpoint with full level alpha will be performed at the primary analysis time point. A final analysis will be performed at the end of the study.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation is based on the primary variable PFS. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.

In the planned study, median PFS of 2.5 months was assumed for the control arm in this study population (Hanna et al 2004, de Marinis and Grossi 2008, Weiss and Stinchcombe 2013, Borghaei et al 2015, Rittmeyer et al 2017) and considering the negative prognostic impact of the MET dysregulation (Dimou et al 2014, Guo et al 2014, Landi et al 2017, Awad et al 2019).

Under the assumption that the median PFS in the control arm is 2.5 months in these participants, it is expected that treatment with capmatinib will result in a 58% reduction in the hazard rate (corresponding to an increase in median PFS from 2.5 months to 6 months under the exponential model assumption). If the true hazard ratio is 0.42 (under the alternative hypothesis), a total of 62 PFS events are required to have 90% power at a one-sided 2.5% level of significance to reject the null hypothesis (HR=1) using a log-rank test. Assuming that enrollment will continue for approximately 19 months with a rate of 3 participants/month for the first half year and 6 participants/months from month 7 onwards, and 20% dropout, approximately 90 participants will need to be randomized to reach the required number of events for the two treatment arms in a 2:1 ratio, 60 participants in the capmatinib arm and 30 participants in the chemotherapy arm. Given the above assumptions, it is estimated that the 62nd PFS event will occur approximately 21 months from the date of first participant randomized in the study. No interim analysis is planned for PFS.

These calculations were performed using the software package East (6.4).

12.8.2 Secondary endpoint(s)

ORR, as the key secondary variable, will be formally statistically tested, provided that the primary variable PFS is statistically significant. The hypotheses to be tested and details of the testing strategy are provided in Section 12.5.1.1.

[redacted]

Based on available data (Borghaei et al 2015, Brahmer et al 2015, Herbst et al 2016, Rittmeyer et al 2017) and considering the negative prognostic impact of the MET dysregulation in the targeted population, the ORR in the control arm is expected to be around 10%. It is hypothesized that treatment with capmatinib will result in a 30% increase in the ORR, i.e., an expected ORR of 40% (Wolf et al 2020). The ORR will be tested at the time of the final PFS analysis. The sample size calculation is based on the number of participants that are planned to be enrolled to provide sufficient power for the primary endpoint (90 participants), the randomization ratio of 2:1, and the hypotheses H_{01}: $\theta_1 - \theta_2 \leq 30\%$ vs. H_{A1}: $\theta_1 - \theta_2 > 30\%$. With these assumptions, the test for the difference in ORR without the stratification factor and with a pooled estimate of variance will have 88.2% power with a one-sided alpha of 0.025.

The approximate treatment difference (Δ ORR) required to reach the boundary for significance (i.e. reject the null hypothesis) is 16.4%.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 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 patient 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.

[redacted]

13.4 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 SOPs, and are performed according to written Novartis processes.

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.

[redacted]

15 References

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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)

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Glossary

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

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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 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Cystic lesions:

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- 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

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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 10mm 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, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal

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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 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.

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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.

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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	

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.

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- 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

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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

[redacted]

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

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).

[redacted]

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 (BOR)

The 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

[redacted]

- 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:

[redacted]

- 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.

[redacted]

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.

[redacted]

[redacted]

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.

[redacted]

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.

[redacted]

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.

[redacted]

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:

[redacted]

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.

[redacted]

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

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (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.

[redacted]

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.

[redacted]

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:

[redacted]

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

[redacted]

- 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.

[redacted]

16.1.5 References (available upon request)

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

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

[redacted]

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

Document type	TA specific guideline
Document status	Version 1: 04-Jun-2020
Release Date	04-Jun-2020
Authors (Version 1)	[redacted]

[redacted]

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

[redacted]

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 8.4.

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.

[redacted]

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.

[redacted]

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 ^{18}FLT 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:

[redacted]

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

[redacted]

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.

[redacted]

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 disease (Non-CR/non-PD)	Persistence of one or more non-target CNS lesion or lesions.
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., ≤ 5 mm), continued therapy can be considered, and a follow-up assessment will clarify 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

[redacted]

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.

[redacted]

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
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). 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.

[redacted]

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.

[redacted]

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
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

[redacted]

- 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.

[redacted]

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.

[redacted]

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.

[redacted]

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)

[redacted]

16.2.4 References

Eisenhauer EA, Therasse P, Bogaerts J et al (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer; 45(2):228-47.

Lin N et al (2015) Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncology, 16:e270-278.

[redacted]

16.3 Appendix 3: List of concomitant medications that require caution or are prohibited for patients on capmatinib

Table 16-11 Medications that require caution when concomitantly used with capmatinib

Mechanism of Interaction	Drug Name
Strong CYP3A inhibitor	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,clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
Moderate CYP3A inducer	bosentan, dabrafenib, efavirenz, etravirine, genistein, modafinil, nafcillin, tipranavir/ritonavir, lopinavir, telotristat, thioridazine
CYP1A2 substrate with NTI	theophylline, tizanidine
P-gp substrates [1]	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, atorvastatin, azithromycin, boceprevir, bosentan, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine, dabigatran, digoxin, docetaxel, doxepin, doxorubicin, eribulin, everolimus, fentanyl, fexofenadine, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, linagliptin, linezolid, loperamide, losartan, maraviroc, mirabegron, moxifloxacin nadolol, naloxegol, nateglinide, nevirapine, nintedanib, olodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, proguanil, quinidine, ranolazine, riociguat, risperidone, ritonavir, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
BCRP substrates [1]	atorvastatin daunorubicin, dolutegravir, doxorubicin, ethinyl estradiol, hematoporphyrin, imatinib, irinotecan, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitor	dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
H_2-receptor antagonists	cimetidine, famotidine, nizatidine, ranitidine
Antacids	aluminum carbonate, aluminum hydroxide, calcium carbonate, calcium hydroxide, 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 (drug-interactions.medicine.iu.edu/Main-Table.aspx), 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 mentioned database for the latest information. NTI: narrow therapeutic index

[1] If coadministration with capmatinib is unavoidable and minimal concentration changes of the drug listed may lead to serious adverse reactions, decrease dosage in accordance with the approved prescribing information.

[redacted]

Table 16-12 Capmatinib: prohibited drugs

Mechanism of Interaction	Drug Name (generic)
Strong CYP3A4 inducer	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (Hypericum perforatum)
Live vaccines	e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines, COVID-19 vaccines
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 (drug-interactions.medicine.iu.edu/Main-Table.aspx), 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 mentioned databases for the latest information.	