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INC280 (capmatinib), EGF816 (nazartinib)

Clinical Trial Protocol CINC280X2105C / NCT02335944

A phase Ib/II, multicenter, open-label study of EGF816 in combination with INC280 in adult patients with EGFR mutated non-small cell lung cancer

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List of abbreviations

Ab	Antibody
Ag	Antigen
ADME	Administration, Distribution, Metabolism and Excretion
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 the concentration-time Curve
BAL	Broncho-Alveolar Lavage
BCG	Bacille Calmette-Guerin
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics Classification System
b.i.d	*bis in die* / twice daily
BIRC	Blinded Independent Review Committee
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
bpm	beats per minute
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CAS	Combination Analysis Set
cfDNA	cell free Deoxyribo-Nucleic Acid
CFR	Code of Federal Regulations
CI	Confidence Interval
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum plasma concentration
CMO&PS	Chief Medical Office and Patient Safety
CMV	CytoMegaloVirus
CNS	Central Nervous System
COVID-19	Corona Virus Disease 2019
CR	Complete Response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization

CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CV	Coefficient of Variance
CYP	Cytochrome P450 Enzymes
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DDS	Dose Determining Set
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DLCO	Diffusing capacity of the Lungs for Carbon monoxide
DLT	Dose Limiting Toxicity
DOR	Duration Of Response
EAS	Evaluable Analysis Set
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; also known as ErbB1
EOT	End of Treatment
ERCP	Endoscopic retrograde cholangiopancreatography
eSAE	electronic Serious Adverse Event
EU	European Union
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
FU	Follow-up
GCN	Gene Copy Number
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GGT	Gamma-Glutamyl-Transferase
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus-DNA
HC Ab	Hepatitis C antibody
hCG	Human Chorionic Gonadotropin

HCV	Hepatitis C virus
HCV-RNA	Hepatitis C virus-RNA
HDPE	High-Density PolyEthylene
hERG	human Ether-à-go-go-Related Gene
Hgb	Hemoglobin
HGF	Hepatocyte growth factor
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
IA	Interim Analysis
IB	Investigator's brochure
IC50	Half maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immuno-histochemistry
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
i.v.	Intravenous(ly)
KRAS	Kirsten RAt Sarcoma viral oncogene homolog
LFT	Liver Functional Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MATE	Multidrug And Toxic compound Extrusion transporter
MCV	Mean Corpuscular Volume
MET	Mesenchymal-to-Epithelial Transition factor
METΔex14	MET exon 14 skipping
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mut	Mutated
NCI	National Cancer Institute
NE	Not Estimable
NGS	Next Generation Sequencing
NRU	Neutral Red Uptake
NSCLC	Non-Small Cell Lung Cancer
NTI	Narrow Therapeutic Index
OATP	Organic Anion Transporting Polypeptide
ORR	Overall Response Rate
OS	Overall Survival

p.o.	*per os*/by mouth
PAS	Pharmacokinetic Analysis Set
PBPK	Physiologically Based PharmacoKinetic
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PFT	Pulmonary Function Test
P-gp	Permeability glycoprotein
PHI	Protected Health Information
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/Pharmacodynamics
PLT	Platelet
PoS	Probability of success
PP	Predictive Probability
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
q.d.	*quaque die*/every day
QTcF	Corrected QT interval using Fridericia correction
RANKL	Receptor Activator of Nuclear factor Kappa-B Ligand
RBC	Red Blood Cell
RP2D	Recommended Phase 2 Dose
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	c-ros oncogene 1
R value	Ratio of ALT to ALP (both expressed as x ULN)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SEC	Safety Event Categories
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedure
T1/2	Terminal elimination half-life
TDAR	T-cell Dependent Antigen Response
TEC	Tyrosine kinase Expressed in hepatocellular Carcinoma
TKI	Tyrosine Kinase Inhibitor
Tmax	Peak plasma concentration
TTR	Time To Response
ULN	Upper Limit of Normal
US	United States
USA	United States of America
USPI	United States Prescribing Information
UV	Ultra-Violet

VATS	Video-assisted thoracic surgery
Vss	Steady state volume of distribution
WCLC	World Conference on Lung Cancer
WoC	Withdrawal of Consent
WT	Wild Type

Glossary of terms

Adjuvant chemotherapy	Anticancer medication administered following initial curative surgery and/or radiotherapy for newly diagnosed early disease (i.e., stages I-II) or optimally debulked advanced disease (stages III and IVa). Chemotherapy administered in these clinical situations will be considered adjuvant, unless there is evidence of disease progression prior to the start of chemotherapy or evidence of persistent macroscopic residual disease after surgery (i.e., non-optimally debulked advanced disease).
Assessment	A procedure used to generate data required by the study
Biological Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant.
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 newly enrolled participants treated at a specific dose and regimen (i.e. treatment group) at the same time.
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g. q28 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 drug 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.
Dose level	The dose of drug given to the participant (total daily or weekly etc.).
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or as defined by the protocol.
Enrollment	Point/time of participant entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol). The action of enrolling one or more participants.
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Investigational drug/treatment	The drug whose properties are being tested in the study.
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.
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study.

Neoadjuvant chemotherapy	Anticancer medication administered prior to initial surgery. Stem cell transplant preparatory regimens should be considered as neoadjuvant.
Palliative care	Any treatment that alleviates pain and discomfort to improve quality of life of participants with end-stage disease. For example, zoledronic acid given to treat the pain from bone metastases or localized radiotherapy to treat pain from-pre-existing bone metastases. These treatments must begin before the initiation of study treatment. Requirement of these treatments during the study is considered a sign of disease progression.
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease.
Participant	A trial participant is a patient who has consented to participate in the study. “Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant Number (Participant No.)	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.
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.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
Screen failure	A participant who did not meet one or more criteria that were required for participation in the study.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Stage 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 clinical trial	The start of the study is defined as the signature of the informed consent by the first participant.
Study treatment	Includes any drug or combination of drugs in any study arm administered to the study participant as part of the required study procedures; includes investigational drug(s), control(s) or background therapy. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Therapeutic setting	A setting of treatment whereby an antineoplastic agent is given to treat the cancer except in the adjuvant and neo-adjuvant setting. For example, targeted therapies (e.g., sunitinib, pazopanib, axitinib, everolimus, temsirolimus, bevacizumab) or immunotherapies (e.g., interferon, interleukin 2), chemotherapies, or hormonal therapies.

Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of Consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent occurs when a participant explicitly requests to stop use of their data and biological samples (opposition to use data and 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. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 07 (20-Oct-2021)

Amendment rationale

As of 20-Oct-2021, a total of 177 participants have been enrolled in the study: 33 participants in Phase Ib and 144 in Phase II (Group 1 to Group 4). All participants from Phase Ib and Phase II Groups 1 to 4 had met one of the end of study completion criteria as considered under protocol amendment 6 and there are no participants receiving treatment.

The main purpose of this amendment is to implement a new participant Phase II Group 5 to determine the efficacy and safety of capmatinib monotherapy. The rationale for this addition is based on the following:

- Based on the preliminary clinical efficacy and safety data observed in NSCLC participants who received capmatinib in combination with nazartinib (a third generation EGFR TKI) therapy in this study, the Sponsor plans to establish the role of capmatinib in combination with the third generation EGF TKI in a population of participants with EGFRm, T790M negative, MET amplified, progressed on prior line of EGFR TKI treatment NSCLC. However, it is necessary to also consider the contribution of components; based on the clinical efficacy and safety data of Study [CINC280A2201] observed in a related population of NSCLC in EGFR WT, METex14 mutated, regardless of line of treatment. Furthermore, the contribution of capmatinib as monotherapy needs to be established in this EGFR mutant setting which then will pave the way for the optimal use of the combination in future trials.
- There is limited data on the safety and efficacy of capmatinib monotherapy in NSCLC EGFR resistant MET amplified (Gautschi et al 2020) supporting further the proposed investigation. From the data provided by Wolf et al. (2020) which indicated that the median time to response for capmatinib was 6 weeks, data from this arm can be adequately regarded as a measure for the contribution of capmatinib monotherapy in this setting and will provide a significant step to further evaluate this new treatment strategy.

The analysis of the primary objective for Phase II Group only was formulated using the estimands framework as the primary analysis and analysis of additional data of Phase Ib and Phase II Groups 1 to 4 had already occurred prior to opening enrollment of Group 5.

Furthermore, the guidelines for management of selected toxicities have been updated to optimize the participant's safety. These changes are not due to new safety findings. The lists of permitted and prohibited concomitant medications have been revised based on periodic update and aligned with the current [capmatinib Investigator's Brochure] and [nazartinib Investigator's Brochure].

Additionally, several protocol sections were amended to provide specific related guidance and clarification with regard to the event of a major healthcare disruption (e.g., a pandemic or epidemic). The assessment of Benefit/Risk concluded the absence of additional risks related to COVID-19 (Corona Virus Disease 2019).

Finally, the background section has been updated with the most recent information gathered throughout the relevant literature and clinical studies results.

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

Changes to the protocol

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

The following changes have been implemented and the protocol has been updated to reflect all significant changes below:

- Based on current Novartis protocol template, wording of "*patient*" and "*subject*" has been updated to "*participant*" throughout the document where appropriate
- Based on current Novartis protocol template, remove wording of "*REB*" (Research Ethics Board) from expression "IRB/IEC/REB" throughout the document where appropriate.
- Based on current Novartis protocol template, "*withdrawal of consent*" replaced by "*withdrawal of informed consent/Opposition to use data/biological samples*" or "*consent withdrawal opposition*"
- Wording of "*BID*" has been updated to "*b.i.d.*" throughout the document where appropriate
- Wording of "*QD*" has been updated to "*q.d.*" throughout the document where appropriate.
- Wording of *"c-MET"* has been updated to "*MET"* throughout the document where appropriate
- Wording of *"INC280"* has been updated to "*capmatinib"* throughout the document where appropriate
- Wording of *"EGF816"* has been updated to "*nazartinib"* throughout the document where appropriate
- Wording of *"AZD9291"* has been updated to "*osimertinib"* throughout the document where appropriate
- Wording of *"phase I", "phase 1" or "part I"* has been updated to "*Phase Ib"* throughout the document where appropriate
- Wording of *"Phase 2" or "part II"* has been updated to "*Phase II"* throughout the document where appropriate
- Language and grammar revised as needed
- Re-numbering of sections due to addition of sections in the new protocol template versions
- Sections referenced modified to align with section changes
- Adding language regarding public health emergencies added where applicable
- Title page: based on current Novartis protocol template, Novartis department has been updated and the list of authors was removed
- Table of contents updated
- List of appendices has been removed as they are listed in the Table of contents
- List of figures updated
- List of tables has been updated
- List of abbreviation has been updated
- Glossary of terms: updated based on current Novartis protocol template

- Protocol summary: updated purpose and rationale, primary and secondary objectives, study design, key inclusion and exclusion criteria, investigational and reference therapy, data analysis based on the changes highlighted in the amendment rationale
- Section 1 Background: updated the whole section to reflect the current clinical and safety evidence
- Section 2.1 Study rationale and purpose:
  - clarified rationale for combination therapy of nazartinib and capmanitib
  - added rationale for capmatinib monotherapy
- Section 2.2 Rationale for the study design: included rationale for inclusion of new Phase II Group 5
- Section 2.3 Rationale for dose and regimen selection: included rationale for capmatinib monotherapy which can be administered with or without food
- Section 2.6 Risks and benefits: added rationale for recommended starting dose of capmatinib monotherapy
- Section 2.7 Rationale for public health emergency mitigation procedures: new section added to align with latest Novartis protocol template in order to provide the rationale for public health emergency mitigation procedures
- Table 3-1 Objectives and related endpoints: updated to add the primary, secondary [redacted] objectives of newly added Phase II Group 5
- Section 4.1 Description of study design: updated to reflect the inclusion of Phase II Group 5
- Figure 4-1 Study design: revised the study flow chart to reflect the implementation of Phase II Group 5
- Section 4.2 Timing of interim analyses and design adaptations:
  - Clarified that interim analysis will be conducted for Phase II Group 3 and 5 participants
  - Added interim analysis for Phase II Group 5 participants
- Section 4.3 Definition of end of study:
  - Added interim CSR to report final analysis of participants in Phase Ib and Phase II Groups 1 to 4
  - Updated the primary analysis and end of study definitions due to the inclusion of Phase II Group 5
  - Clarified post trial access of study medication if participant continues to demonstrate clinical benefit
- Section 4.4 Early study termination: updated to align with other Novartis-sponsored study protocols
- Section 5.1 Study population:
  - Updated sub-section title to align with latest Novartis protocol template
  - Updated to define Phase II Group 5 participant population
- Section 5.2 Inclusion criteria:
  - Updated inclusion criterion 3, 4, 9 for enrollment into Phase II Group 5

  - Added includion criterion 15 for enrollment into Phase II Group 5
  - Added inclusion criterion 16 for participants to have a life expectancy of at least 3 months to align with the program standard language
  - Added inclusion criterion 17 for participants willing and able to comply with scheduled visits, treatment plan and laboratory tests to align with the program standard language
- Section 5.3 Exclusion criteria:
  - Updated exclusion criterion 2, 4, 6, 13. 15, 17 and 19 for enrollment into Phase II Group 5
  - Clarify exclusion criterion 5 for safety concerns or compliance
  - Added exclusion criterion 24 for participants with known hypersensitivity to capmatinib or nazartinib, or any excipient of these agents
  - Added exclusion criteria 27 to include requirement for specific timing of receiving a live vaccine prior to starting study treatment
  - Clarified the exclusion critera 8 to include HIV participants only when the disease is under control, the suppressed viral loads as defined by local guidelines and on established ART for at least four weeks prior to enrollment.
  - Updated exclusion criteria 10 as per updated safety guidance
  - Updated exclusion criteria 16 for the CTCAE version used for Phase II Group 5 participants
  - Clarified exclusion criteria 19 for for QT interval prolongation and/or Torsades de Pointe
  - Updated exclusion criterion 22 and 23 to align with latest Novartis protocol template
  - Added exclusion criterion 25 and 26 for enrollment into Phase II Group 5
  - Added exclusion criterion 27 to exclude participants with live vaccines injection within 30 days prior to the first dose of study treatment
- Section 6.1 Study treatment: updated the study treatment for newly added Phase II Group 5
- Table 6-1 Dose and treatment schedule:
  - Removed dose strength of 50 mg for Capmatinib as this was never produced and used in the study
  - Added footnote for Phase II Group 5 participants
- Section 6.1.1 Dosing regimen
  - Added dosing regimen requirement for Phase II Group 5 participants
  - Added food conditions for Phase II Group 5 participants
- Section 6.1.2 Treatment duration:
  - Updated language for withdrawal of consent/opposition to use data/biological samples to align with other Novartis-sponsored study protocols
  - Added treatment duration for Phase II Group 5 participants
  - Added guidance for treatment beyond progression disease from the investigator judgement
- Section 6.3.1 Dose modification and dose interruption

- Clarified the criteria for dose re-escalation
- Clarified that events not included in the study protocol or the reference guidance documents should be managed according to local practices
- Replaced Table 6-5 of "recommended dose reduction steps for the Phase II part" by "dose reduction steps for capmatinib"
- Added new Table 6-6 for "dose reduction steps for nazartinib"
- Updated Table 6-7 entirely to align with the latest safety guidelines
- Added new Table 6-8 for "Dose modifications for capmatinib monotherapy (or if nazartinib permanently discontinued and capmatinib continued as monotherapy)"
- Added new Table 6-9 for "Dose modifications for nazartinib (if capmatinib permanently discontinued and nazartinib continued as monotherapy)"

- Section 6.3.2 Guidelines for screening, monitoring and management of HBV / HCV reactivation (including Table 6-10, Table 6-11, Table 6-12): updated the monitoring of HBV-DNA from every 12 weeks to every 4 weeks and monitoring of HVC-RNA from every 8 weeks to every 4 weeks as per new safety guidance
- Section 6.3.4 Follow-up for toxicities:
  - Clarify that unscheduled assessment should be performed in all cases where toxicity monitoring is recommended more frequently than defined by the schedule of assessments
  - Added Table 6-16 Toxicity follow-up evaluation
- Section 6.3.4.1 Follow up on potential QTcF prolongation: added a follow-up action in case of QTcF >500 ms and after confirming ECG reading at site, if QTcF > 500 ms
- Section 6.3.4.2 Follow up on potential drug-induced liver injury (DILI) cases:
  - Updated as per latest safety guidelines
  - Added Table 6-17 for guidance to rule out other alternative causes of observed LFT abnormalities
- Section 6.4.1 Permitted concomitant therapy: clarified that each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication as per latest Novartis template
- Section 6.4.1.1 Permitted concomitant therapy of capmatinib in combination with nazartinib:
  - Added sub-title
  - Move paragraph on use of bisphosphonates from this sub section to new sub section 6.4.4.
- Section 6.4.1.2 Permitted concomitant therapy of capmatinib monotherapy in Phase II Group 5: added sub-section due to the addition of Phase II Group 5
- Section 6.4.2.1 Permitted concomitant therapy of capmatinib in combination with nazartinib requiring caution and/or action:
  - Added sub-title
  - Clarification on the classification of the medications

- Section 6.4.2.2 Permitted concomitant therapy of capmatinib monotherapy requiring caution and/or action in Phase II Group 5: added sub-section due to the addition of Phase II Group 5
- Section 6.4.3 Prohibited concomitant therapy: added sentence that if during the course of the trial prohibited concomitant medication cannot be avoided study treatment must be interrupted until an assessment of the potential safety risk has been performed
- Section 6.4.3.1 Prohibited concomitant therapy with capmatinib and nazartinib:
  - Added sub-title
  - Clarified the language to prohibit "live" vaccine during the trial (including COVID-19 vaccines)
  - Section 6.4.3.2 Prohibited concomitant therapy with capmatinib monotherapy in Phase II Group 5: added sub-section due to the addition of Phase II Group 5
- Section 6.4.4 Use of bisphosphonates or RANKL inhibitor: added new sub-section
- Section 6.4.5 Permitted radiotherapy: added new sub-section
- Section 6.5.1 Participant numbering: Replaced Oracle RDC by EDC interface (generic term)
- Section 6.5.2 Treatment assignment: updated to define Phase II Group 5 treatment assignment
- Section 6.6 Study drug preparation and dispensation: added language regarding public health emergencies
- Section 6.6.1 Study drug packaging and labeling: updated to define Phase II Group 5 drug packaging and labeling
- Section 7.1 Study flow and visit schedule:
  - Added language regarding public health emergencies
  - Updated Table 7-1 title to "Visit evaluation schedule for Phase Ib and Phase II Groups 1 to 4"
  - Added Table 7-2 for "Visit evaluation schedule for Phase II Group 5"
- Section 7.1.1 Molecular pre-screening:
  - Clarified Met dysregulation definition for Phase II Group 5 participants
  - Added Phase II Group 5 EGFRm and Met dysregulation documentation requirements
- Section 7.1.2 Screening: update screening requirements for Phase II Group 5 participants
- Section 7.1.2.1 Information to be collected on screening failures: added requirements to be collected for screen failed participants in Phase II Group 5
- Section 7.1.3 treatment period: updated language for withdrawal of consent/opposition to use data/biological samples to align with other Novartis-sponsored study protocols
- Section 7.1.4 Discontinuation from study treatment and from study:
  - Update sub-title to "Discontinuation from study treatment and from study" as per latest Novartis protocol template
  - Updated language for withdrawal of consent/opposition to use data/biological samples to align with other Novartis-sponsored study protocols
  - Clarified participants who discontinue from study treatment definition

  - Added discontinuation from study definition
- Section 7.1.5 Withdrawal of informed consent/Opposition to use data/biological samples:
  - Updated sub-title to Withdrawal of consent/Opposition to use data/biological samples as per latest Novartis protocol template
  - Updated withdrawal of consent language and definition as per latest Novartis protocol template
  - Added paragraph on Personal and Coded data as per Novartis protocol template
- Section 7.1.6: Follow-up for safety evaluations: Updated the survival follow-up paragraph as not applicable for participants in Phase II Group 5.
- Section 7.1.7 Lost to follow-up: Clarified withdrawal, discontinuation from study treatment and discontinuation from study language as per latest Novartis protocol template
- Section 7.2.1 Efficacy assessments:
  - Clarified that BIRC evaluation may be used except for Phase II Group 5
  - Added language for re-baseline requirements to enter extension part for Phase II Group 5 participants
  - Table 7-3 Imaging collection plan: updated to include requirements of EoT/Re-baseline for Phase II Group 5 participants
  - Added language regarding public health emergencies
- Section 7.2.2 Safety and tolerability assessments: added language regarding public health emergencies
- Section 7.2.2.1 Physical examination:
  - Clarified physical examination for Phase II Group 5
  - Added reference to newly added table 7-2
- Section 7.2.2.2 Vital signs: added reference to newly added table 7-2
- Section 7.2.2.3 Height and weight: added reference to newly added table 7-2
- Section 7.2.2.4 Performance status:
  - Rephrase definition of ECOG
  - Added reference to newly added table 7-2
- Section 7.2.2.5 Laboratory evaluations:
  - Added that for Phase II Group 5 laboratory evaluations will be done locally
  - Added reference to newly added table 7-2
  - Added language regarding public health emergencies
- Section 7.2.2.5.1 Hematology: added reference to newly added table 7-2
- Section 7.2.2.5.2 Clinical chemistry: added reference to newly added table 7-2
- Section 7.2.2.5.3 Coagulation: added reference to newly added table 7-2
- Section 7.2.2.5.4 Urinalysis: added reference to newly added table 7-2
- Section 7.2.2.5.5 HBV and HCV testing: added reference to newly added table 7-2
- Section 7.2.2.5.6 Pregnancy and assessments of fertility: added language regarding public health emergencies

- Section 7.2.2.6 Cardiac assessments:
  - Added reference to newly added Table 7-2 and Table 7-6
  - Table 7-6: Added a note that PK post dose are not applicable for new Group 5
- Section 7.2.3 Pharmacokinetics: added a note that no PK samples will be collected for newly added Group 5
- Section 7.2.4 Biomarkers: added language regarding public health emergencies
- Section 7.2.4.1 Biomarker assessments in tumor:
  - Clarified the assessments performed for newly added Group 5 and marked the others as Not Applicable
  - Updated the section to allow Met amplication status determined also by local testing with retrospective central testing for Phase II Group 5
- Section 7.2.4.2: updated Table 7-11 for biomarker sample collection in newly added Group 5
- Section 8 Safety monitoring, reporting and committees: updated title as per latest Novartis protocol template
- Section 8.1.1 Definitions and reporting:
  - Updated AE definition as per Novartis protocol template
  - Clarified non reporting of SAE in case of progression of malignancy as per latest Novartis protocol template
  - Updated CTCAE version to 5.0 for new Phase II Group 5
- Section 8.1.3 Adverse event of special interest: remove list of AESI from the protocol as this is referenced in the IB
- Section 8.2.2 SAE reporting:
  - Update sub title as per latest Novartis protocol template
  - Clarified immediate reporting to align with health authority requirements as per latest Novartis protocol template
- Section 8.3 Pregnancy reporting:
  - Updated sub-title to align with latest Novartis protocol template
  - Updated Pregnant Participants and Pregnant Partners language for clarity as per latest Novartis protocol template
- Section 8.5 Data Monitoring Committee:
  - Clarified that the interim analysis written in the protocol was for Phase II Group 3
  - Added interim analysis for newly added Phase II Group 5
- Section 9 Data collection and database management: updated title as per latest Novartis protocol template
- Section 9.1 Data Confidentiality: Clarified key sensitive personally identified information as per latest Novartis protocol template
- Section 9.4 Database management and quality control:
  - Updated the method for archiving participant data at the investigational site
  - Updated the database lock wording as per the new Novartis protocol template

- Section 10 Statistical methods and data analysis:
  - Updated rules for reporting results due to the addition of Phase II Group 5
  - Added language regarding public health emergencies
- Section 10.1 Analysis sets for Phase Ib and Phase II Groups 1 to 4: updated title to reflect the applicability to Phase Ib and Phase II Groups 1 to 4
- Section 10.1.2 Safety Set: update reporting document from RAP to SAP as per updated process
- Section 10.1.3 Per-Protocol Set: update reporting document from RAP to SAP as per updated process
- Section 10.2 Analysis sets for Phase II Group 5: added new section for the analysis of newly added Phase II Group 5
- Section 10.5 Primary objective for Phase Ib and Phase II Groups 1 to: updated title to reflect the applicability to Phase Ib and Phase II Groups 1 to 4
- Section 10.5.2.2 Phase II: removal of the sentence to have the possibility of different primary analysis for Groups 1 to 4
- Section 10.6 Primary objective for Phase II Group 5: new section to define the primary objective of newly added Phase II Group 5
- Section 10.7.1.1 Analysis set and grouping for the analyses:
  - Clarified that existing text was for Phase Ib and Phase II groups 1 to 4
  - Updated to add safety summaries for Phase II Group 5 for secondary objectives
- Section 10.7.1.3 Laboratory abnormalities: updated CTCAE version to 5.0 for new Phase II Group 5
- Section 10.7.2 Efficacy objectives: clarified analysis sets used for each efficacy analysis
- Section 10.7.2.1 Secondary efficacy endpoints for Phase Ib and Phase II Groups 1 to 4: updated title to reflect the applicability to Phase Ib and Phase II Groups 1 to 4
- Section 10.7.2.2 Secondary efficacy endpoints for II Group 5: new section to define the secondary efficacy endpoints of newly added Phase II Group 5
- [redacted]
- Section 10.9 Interim analysis: Added interim analysis for newly added Group 5
- Table 10-3 Predictive probability (PP) for ORR of capmatinib monotherapy at the final analysis based on various numbers of responders observed at the IA for Group 5: added new table for newly added Phase II Group 5 interim analysis
- Section 10.10 Sample size calculation:
  - Updated the approximate number of participants to be enrolled in Phase II with the addition of 30 participants in Group 5
  - Added paragraph for Group 5 sample size calculation
  - New table 10-7 for Operating characteristics for various assumed true ORR of capmatinib monotherapy
- Section 11.3 Informed consent procedures:

  - Clarified that male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study
  - Added language regarding public health emergencies
- Section 13: updated the reference list as appropriate
- Section 14.3: Appendix 3
  - Update Table 14-14 name to clarified that it applied to the combination therapy
  - Added Table 14-15 to list the permitted concomitant medication requiring caution with Capmatinib monotherapy in Phase II Group 5
- Section 14.4: Appendix 4
  - Update Table 14-16 name to clarified that it applied to the combination therapy
  - Table 14-16: Clarified the language to prohibit "live" vaccine during the trial (including COVID-19 vaccines)
  - Added Table 14-17 to list the prohibited concomitant medication requiring caution with Capmatinib monotherapy in Phase II Group 5

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 06 (11-Apr-2017)

Amendment rationale

As of 31-Mar-2017, a total of 93 patients have been enrolled in the study. In the phase Ib dose escalation part, 33 patients have been enrolled. The phase II expansion part was opened for enrollment in March 2016 and 60 patients have been enrolled (54 patients in Group 1 [EGFRm, any T790M, any c-MET, 2/4L NSCLC, EGFR TKI resistant], 2 patients in Group 2, [de novo T790M+, any c-MET, 1/3L NSCLC, EGFR TKI-naïve], and 4 patients in Group 3 [EGFRm, T790M negative, any c-MET, 1L NSCLC]). All patients enrolled in the Phase II part have received the recommended phase 2 dose (RP2D), i.e., INC280 400 mg BID + EGF816 100 mg QD. As of 19-Dec-2016, enrollment in phase II group 1 was completed.

The main purpose of this amendment is to add in phase II a new group 4 of patients (N=30) with EGFRmut, any T790M, any c-MET, in order to assess the safety and tolerability of the combination therapy when taken with food (unrestricted meal type). Patients must have locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del), be treatment-naïve for advanced disease (1L) or have failed (defined as intolerance to treatment or documented disease progression) a maximum of 2 prior lines of systemic antineoplastic therapies in advanced setting (2/3L) prior to study entry.

Safety data from phase Ib part of this study showed high frequency of upper gastrointestinal (GI) adverse effects (AEs) with nausea (62.5%), vomiting (31.3%) being some of the most common AEs when combination therapy INC280/EGF816 was administered at the RP2D of INC280 400mg BID/EGF816 100 mg QD on fasting conditions. Fasting condition is defined as fasting from food at least one hour before and two hours after a meal [INC280 Investigator's Brochure, edition 7]. The majority of GI events were of CTCAE grade 1 or 2 and were managed with standard approaches, including anti-emetics.

In comparison the incidence of gastro intestinal AEs with currently approved therapy, such as erlotinib, a first generation EGFR TKI, is lower for nausea (33%) and vomiting (23%).

To improve the tolerability profile of the combination therapy, it is proposed in this new group 4 to administer study medication with food, as dosing with food has been shown to improve the GI tolerability of some multi-kinase inhibitors such as imatinib (Gleevec®) and bosutinib (Bosulif®). Imatinib does not exhibit a food effect, although it is recommended that imatinib be taken with food to minimize GI irritation (Gleevec® prescribing information). In a food-effect trial, a high-fat meal increased bosutinib exposure by 2-fold. Bosutinib showed better tolerability when co-administered with food; as a result, bosutinib was co-administered with a meal in patient trials and is advised to be taken once daily with food in the label (Bosulif® prescribing information).

In the current study, EGF816 and INC280 combination is administered on an empty stomach defined as fasting from food at least one hour before or two hours after a meal. Preliminary PK results at RP2D (EGF816 100 mg QD/INC280 400 mg BID) showed that INC280 steady-state exposure (AUC,ss) is similar to those observed in single-agent studies with INC280, whereas EGF816 AUC,ss is ~35% higher compared to the exposure observed in the single agent study with EGF816. Similar extent of EGF816 AUC,ss increase is also observed when combined with

INC280 200 mg BID, indicating that EGF816 exposure increase may have reached a plateau when combined with INC280 at dose of 200 mg BID or higher.

No dedicated food effect study has been conducted for EGF816. EGF816 was predicted to be a highly permeable compound based on the results from Caco-2 cell monolayer study. The *in vitro* solubility is excellent over the pH range tested (pH range 1 to 6.8) and in simulated intestinal fluid for both fasted and fed state. Therefore, it is characterized as biopharmaceutics classification system (BCS) class I compound with low food effect risk. In the ongoing single agent EGF816 study [EGF816X2101], EGF816 can be administered with or without food.

[redacted]

For Phase II Group 4 (EGFRm, any T790M, any c-MET, 1L (treatment naive) 2/3L antineoplastic), patients will be given INC280/EGF816 combination with food. Based on the food-effect result in healthy volunteer, the steady state exposure increase of INC280 when given with food is expected to be 11-46% compared to the exposure observed under fasted condition. It is unlikely that an increase of INC280 exposure with food will lead to further increase of EGF816 exposure given that interaction between INC280 and EGF816 seems to have reached a plateau at INC280 dose of 200 mg BID or higher and the MTD has not been reached with INC280 given at 400mg BID under fasted condition.

Given the known safety profile of INC280/EGF816 combination, their known or expected food effect, and the observation that food has improved the GI tolerability of other multi-kinase inhibitors, this Phase II Group 4 will evaluate the safety and PK of INC280 400mg BID + EGF816 100 mg QD when administered with food.

Furthermore, amendment 6 implements other substantial changes as follows:

- Update related to INC280 safety: updates were made in the clinical overview section based on the most current Investigator's Brochure edition 7 (cut-off date 28-Sep-2016).
- Provide preliminary data in Section 1.2.3.2 about clinical experience of INC280 and EGF816 combination treatment
- Corrected the exclusion criterion for patients with asymptomatic serum amylase and lipase > Grade 2, to clarify that patient will now meet exclusion criterion even if only one of the two parameters (asymptomatic serum amylase or lipase) is > Grade 2.
- Added the collection of an optional on-treatment biopsy with paired cfDNA sample to identify emergence of potential resistance markers during treatment as well as understand the correlation between tissue and plasma biomarker status.

Other non-substantial changes were made to provide more clarity to the protocol:

- Clarifies the exclusion criterion for patients with brain metastases.
- Clarifies the interpretation of study discontinuation after dose interruption

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
  - Updated RAP to SAP in this section and throughout the document
- Protocol summary
  - Updated study design, key inclusion and exclusion criteria, study objectives, data analysis based on the changes highlighted in the amendment rationale
  - Corrected exclusion criterion on Creatinine Clearance to align with Section 5.3
- Section 1.2.1 Overview of INC280 (capmatinib)
  - Updated according to last version of the INC280 Investigator's Brochure (Ed. 7, data cut-off date 28-Sep-2016)
  - Clarified the SAE related to cough and shortness of breath to add more clinical information
- Section 1.2.2 Overview of EGF816
  - Updated with most recent efficacy data from the single agent trial
- Section 1.2.3. Overview of INC280 and EGF816
  - New section added to provide preliminary clinical safety and efficacy data on phase Ib patients of the current study as of 01-Aug-2016
- Section 2.1 Study rationale and purpose
  - Editorial changes and clarified that data are related to 1st and 2nd generation EGFR-TKI
  - Updated the word cMET amplification to cMET dysregulation because both amplification and overexpression are mechanism of resistance; this update was done throughout the document
- Section 2.2 Rationale for the study design
  - Added in Group 2 that dual TKI inhibitor are excluded to align with the rest of the protocol
  - Included rationale for inclusion of new phase II group 4 receiving the combination therapy in non-fasted conditions
- Section 2.5 Rationale for choice of comparator drugs
  - New section added to align with other Novartis-sponsored study protocols; this section is not applicable for this clinical study
- Section 2.6 Risks and Benefits
  - New section added to align with other Novartis-sponsored study protocols in order to provide summary of risks and benefits of the combination treatment
- Table 3-1 Objectives and related endpoints
  - Updated to add the primary objective of newly added phase II group 4
  - Clarified that efficacy analysis is based on investigator's assessment

  - Updated the secondary objective and endpoint due to phase II group 4 addition
- Section 4.1 Description of study design
  - Updated to reflect the inclusion of phase II group 4
  - Clarified the tissue sample requirement for phase II group 4
  - Clarified that enrollment of treatment-naïve patients will be prioritized in phase II group 3 and de novo T790M patients enrollment be prioritized in phase II Group 4 and that this allocation will be managed via IRT
- Section 4.2 Timing of interim analyses and design adaptations
  - Clarified that interim analysis will only be conducted for phase II group 3 patients
  - Clarified that if futility is concluded enrollment of treatment-naïve patients in groups 3 and 4 may be stopped while enrollment in other opened groups of pre-treated patients will continue
- Section 4.3 Definition of end of study
  - Clarified that the primary analysis for the different groups may occur at different times due to the expected difference in enrollment completion for each group
- Figure 4-1 Study design
  - Revised the study flow chart to reflect the implementation of phase II Group 4
- Section 5-1 Patient population
  - Updated to define phase II Group 4 patient population
- Section 5-2 Inclusion criteria
  - Added inclusion criterion for enrollment into phase II group 4
- Section 5-3 Exclusion criteria
  - Added exclusion criterion for enrollment into phase II group 4
  - Clarified criterion for patients with brain metastases and removed the discrepancy regarding the washout period for brain radiotherapy (2 weeks required for brain radiotherapy)
  - Updated criterion for asymptomatic serum amylase and lipase
  - Clarified that presence of other malignancies is also an exclusion criterion
  - Clarified that completely resected basal or squamous cell carcinoma are exceptions
  - Removed the washout period for the whole brain radiotherapy
- Section 6.1.1 Dosing regimen
  - Added dosing regimen requirement for phase II group 4 patients
  - Clarified that full PK will be performed at C1D1 and C2D1 on first ten phase II group 3 patients and approximately 20 patients in phase II group 4
- Section 6.3.1 Dose modification and dose interruption
  - Clarified the criteria for dose modification, interruption and dose reduction steps
  - Table 6-6 updated to clarify that patients with combined elevated AST/ALT and total bilirubin must be discontinued
- Section 6.5.2 Treatment assignment

  - Added phase II group 4
  - Clarified the difference between groups 4 and the remaining groups in terms of fasting conditions
- Section 7-1 Study Flow and Visit schedule
  - Added meal recording on C1D1 and C2D1 for full PK patients in the visit evaluation schedule table
  - Added optional on treatment biopsy
  - Added optional whole blood sample (to be paired with optional on treatment biopsy)
- Section 7.1.1 Molecular pre-screening
  - Added phase II group 4 EGFRm documentation requirement
  - Clarified that the tumor sample to be provided can be newly obtained or archival
  - Added the timepoint of tumor sample collection
- Section 7.2.1 Efficacy assessments
  - Updated to clarify that the results of the central Blinded Independent Review Committee (BIRC) evaluations may be used for secondary analyses purposes
- Section 7.2.3.3 Pharmacokinetics sampling during Phase II part
  - Addition of full PK sampling for approximately 20 patients in phase II Group 4
  - Added that the remaining phase II group 4 patients will have sparse PK
  - Updated Tables 7-7 and 7-8 according to above-mentioned changes
- Section 7.2.4.1 Biomarker assessment in tumor
  - Clarify that archival or newly obtained biopsy should be available at time of prescreening
  - Addition of optional on treatment biopsy
  - Addition of optional blood sample to be taken if an optional on treatment biopsy is performed
  - Updated Table 7-10 for phase II group 4 patients and addition of optional on-treatment biopsy and paired optional cell-free DNA
- Section 8.1.3 Adverse event of special interest
  - New section added to align with other Novartis-sponsored study protocols and clarify the AEs of special interest for the combination therapy
- Section 8.2.2 Reporting
  - Changed Novartis pharmacovigilance group name from Drug Safety Epidemiology department to Chief Medical Office and Patient Safety department
- Section 10 Statistical methods and data analysis
  - Addition of phase II Group 4
  - Clarified within the entire Section 10 that primary analysis in the different groups may occur at different times due to expected difference in enrollment completion
  - Clarified that if required, additional analysis sets will be defined in the Statistical Analysis Plan (SAP)

- Section 10.1
- Section 10.1.2 Safety Set
  - Clarified that one dose means one dose of any component of the study treatment
- Section 10.1.5 Pharmacokinetic analysis set for INC280/EGF816
  - Added INC280 and EGF816 to the header to clarify that an analysis sets per investigational drug will be created
  - Clarified the definition of PK evaluability
- Section 10.1.6 Full pharmacokinetic analysis set for INC280/EGF816
  - New section added to clarify the definition of the Full pharmacokinetic analysis set and PK profile evaluability
- Section 10.4 Primary objective
  - Added the primary objective, the definition, and number of patients in Group 4
- Section 10.4.1 Variable
  - Added the variable analyzed for Group 4
- Section 10.4.2.2 Phase II
  - Added the planned analysis of frequency of AEs for Group 4
- Section 10.5.2.1 Secondary efficacy endpoints
  - Added ORR as secondary efficacy endpoint for Group 4
  - Clarified that if available, the results of the central evaluations by BIRC may be used for secondary analyses purposes
- Section 10.5.3 Pharmacokinetics
  - Added the planned PK analysis for Group 4 and its comparison with PK data in fasting conditions
  - Clarified how the concentration data will be listed and summarized
  - Table 10-1 units of the parameters were updated
- Section 10.7 Interim Analysis
  - Clarified that enrollment of treatment-naïve patients may be stopped if futility is concluded
  - Added for PoS 0.14 the number of responders i.e. 9/20
- Section 10.8 Sample size calculation
  - Updated the approximate number of patients to be enrolled in phase II with the addition of 30 patients in group 4
  - Clarified that credible intervals are based on the posterior distribution for different observed number of responses and not on different assumed true observed number of responses (also updated Table 10-3)
  - Added rationale for full PK patients sample size in phase II group 4
  - New Table 10-5 introduced to provide the expected 90% confidence interval
- Section 11.5 Publication
  - Updated to align with Novartis-sponsored study protocols

- Section 13 Appendices
  - Added new cited references
- Section 14.1 – Appendix 1
  - Updated to include most recent guidelines for response version 3.2 dated 11-Feb-2016 based on RECIST 1.1

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 05 (29-Jul-2016)

Amendment rationale

As of 11-Jul-2016, in the Phase I part (dose-escalation) of the study, 33 patients have been enrolled from 7 sites in 6 countries in 7 cohorts using 5 different dose levels. On 23-Feb-2016, during the fifth dose-escalation teleconference, the Recommended Phase 2 Dose (RP2D) was discussed with all Investigators participating in the Phase I part and Novartis. As per protocol, before a drug dosage can be declared to be the Maximum Tolerated Dose or the RP2D, at least six patients should have been treated at that dosage. Among the eleven first patients who received INC280 400 mg BID + EGF816 100 mg QD during the dose-escalation part of the study, one of them experienced a Dose Limiting Toxicity. The other ten patients generally tolerated the treatment. Therefore, based on the available safety, pharmacokinetic and efficacy data and on the Bayesian Logistic Regression Model conclusions, the Investigators and Novartis agreed to declare the RP2D at the dose level of INC280 400 mg BID + EGF816 100 mg QD.

The Phase II part (expansion phase) of the study was opened for enrollment in March 2016. As of 11-Jul-2016, 14 patients had started the study treatment. All patients enrolled in the Phase II part will receive the RP2D, i.e., INC280 400 mg BID + EGF816 100 mg QD.

The main purpose of this amendment is to better define the patient population to be enrolled in the Phase II part of the study (expansion phase). A new group is being added (Group 3), and the sample size of Group 2 is being revised.

Each group has a different patient population determined by specific and mutually exclusive EGFR mutations and the number of prior lines of systemic antineoplastic therapy:

- Phase II Group 1 (EGFRmut, any T790M, any c-MET, 2/4L antineoplastic, EGFR TKI resistant):
  - Locally advanced or metastatic NSCLC with EGFR activating mutation (L858R and/or ex19del) who received one to three lines of systemic antineoplastic therapy prior to study entry including one line maximum of 1st or 2nd generation EGFR TKI (e.g. erlotinib, gefitinib, afatinib) and who progressed on this EGFR TKI treatment line.
  - The presence or the absence of the EGFR T790M mutation is associated with different prognosis. Therefore, the sub-groups are being detailed to account for the different EGFR T790M resistance mutation status, and the statistical analyses will be independently performed on the patients harboring the T790M mutation (minimum of 20 patients), and on the patients not harboring the T790M mutation (minimum of 20 patients). Furthermore, the decision criterion for the analysis of all 40 patients in Group 1 is being removed.
- Phase II Group 2 (EGFRmut, de novo T790M, any c-MET, 1/3L antineoplastic, EGFR TKI naïve):
  - Locally advanced or metastatic NSCLC with a “de novo” EGFR T790M mutation who are treatment naïve or received a maximum of two lines of systemic antineoplastic therapy prior to study entry but no therapy known to inhibit EGFR.
  - The estimated incidence of “de novo” T790M mutation is low (<1% of all lung cancer). Therefore, the sample size is being revised from ≥ 20 to approximately 5 patients if any

identified before the enrollment in Group 1 and Group 3 is complete. The purpose of Group 2 is to collect preliminary safety and efficacy data in this rare patient population.

- Phase II Group 3 (EGFRmut, T790M negative, any c-MET, 1L antineoplastic):
  - Locally advanced or metastatic NSCLC with EGFR activating mutation (L858R and/or ex19del) who never received any prior line of systemic antineoplastic systemic therapy prior to study entry.
  - New group, N≥40 patients.
  - EGF816 is a 3rd-generation irreversible EGFR TKI that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M), while sparing wild type EGFR. Inhibitors of EGFR-mutant L858R and ex19del, such as 1st and 2nd generation EGFR TKIs, have been well validated as therapeutic agents for advanced NSCLC patients who are treatment naive. Based on the mechanism of action, EGF816 will likely have similar clinical activity in this patient population. Despite high response rates to EGFR TKIs, most patients with EGFR-mutant NSCLC ultimately relapse (Kobayashi 2005). Dysregulation of the c-MET pathway is implicated as a therapeutically tractable resistance mechanism. MET is amplified in 21% of NSCLCs with EGFR TKI resistance, and dysregulated in 57% of EGFR-mutant NSCLC patients (Bean 2007, Huang 2014). INC280 is being studied in combination with gefitinib and has shown 50% ORR in patients with c-MET highly amplified (GCN ≥6) NSCLC resistant to EGFR TKIs (Wu 2016). Therefore, it is expected that the co-administration of a highly potent c-MET inhibitor with an EGFR TKI will prevent the development of resistance in the first line setting. Group 3 will allow to explore the hypothesis that targeting the activating resistance mutants together with the two main EGFR resistance mechanisms, T790M and c-MET, may prevent the acquisition of resistance to EGFR TKIs. A sample size of fourty patients will provide acceptable operating characteristics to assess the preliminary anti-tumor activity of the study treatment.
  - An interim analysis for futility is implemented in this patient group (performed on approximately 20 patients). It will allow stopping the enrollment or treatment of the patients in case lack of efficacy is concluded.

Furthermore, Amendment 5 implements other substantial changes as follows:

- Introduces the Recommended Phase 2 Dose and the dose reduction steps starting from the RP2D.
- Implements a requirement of ECOG performance status of 0-1 for all patients to be enrolled in the study to ensure that patients will be able to receive potential benefit from study treatment. It has been well documented that performance status is among the most important prognostic factors for survival of patients with NSCLC.
- Removes the exclusion criterion on fasting plasma glucose ≥160 mg/dL (≥8.9 mmol/L) in the absence of evidence of impact on the glycemia in light of the most recent available clinical data and according to the latest versions of INC280 and EGF816 Investigator Brochures (INC280: Ed. 6, data cut-off date 28-Sep-2015. EGF816: Ed. 5, clinical data cut-off date 18-Dec-2015, safety data cut-off date 27-May-2016).
- Introduces a new dose strength (150 mg) for INC280 tablets.

- Introduces other rare EGFR activating sensitizing mutations that are also considered for enrollment onto the Phase II. These rare mutations, L861Q, G719X, and S768I, account for almost 10% of the cases whereas L858R point mutation and exon 19 deletions account for approximately 90% of the cases.
- Updates the overview of INC280 and EGF816 according to last Investigator Brochure versions (INC280: Ed. 6, data cut-off date 28-Sep-2015. EGF816: Ed. 5, clinical data cut-off date 18-Dec-2015, safety data cut-off date 27-May-2016).
- Removes the restriction of proton pump inhibitors use during the course of the study. INC280 is known to exhibit a pH-dependent solubility profile with a low solubility at high pH levels (Section 3.1 in the current INC280 Investigator's Brochure). [redacted] Daily treatment of [redacted] mg rabeprazole for 4 days resulted in a modest reduction in the extent of INC280 absorption with a [redacted]% decrease in AUCinf and a [redacted]% decrease in Cmax. Considering the [redacted] and [redacted] variability in AUC observed in patients treated in single agent studies [redacted] and [redacted] a decrease of approximately [redacted] in AUC of INC280 when administered with proton pump inhibitor (PPI) is not considered clinically significant. Preliminary data in NSCLC patients ([redacted]) indicated that maintaining plasma trough concentrations above certain threshold over time was required for efficacy. [redacted] Therefore, the concomitant use of PPIs is unlikely to have an impact on the efficacy of INC280, and the PPI restriction as a concomitant medication can be removed from this protocol for patients requiring PPI gastric protection treatment.

Other non-substantial changes were made to provide more clarity to the protocol:

- Clarifies the conditions in which local laboratory assessments should be reported in the Case Report Form during the Phase 2 part of the trial.
- Clarifies the time window for post-dose ECG during the visits with PK sampling.
- Clarifies the definition of acquired resistance mechanisms and the definition of the 4 subgroups of patients being enrolled in the Phase II Group 1.
- Clarifies the biosample requirements for the optional biomarker assessments

Changes to the protocol

- Protocol summary
  - Updated purpose and rationale, study design, inclusion and exclusion criteria, data analysis according to the main changes provided in the protocol
- Section 1.2.1 Overview of INC280 (capmatinib)
  - Updated according to last version of the Investigators' Brochure (Ed. 6, data cut-off date 28-Sep-2015)
- Section 1.2.2 Overview of EGF816
  - Updated according to last version of the Investigators' Brochure (Ed. 4, data cut-off date 18-Dec-2015)

- Section 2.1 Study rationale and purpose
  - Provided complementary information on 3rd generation EGFR TKIs mechanism of action
- Section 2.2 Rationale for the study design
  - Developed rationale for Phase II Group 1 and Phase II Group 2 analyses.
  - Added definition and rationale for Phase II Group 3 analyses.
- Table 3-1 Objectives and related endpoints
  - [redacted]
  - Added footnote with definition of ORR, DCR, TTR, PFS, OS
- Section 4.1 Description of study design
  - Added note to allow for continuation of study drugs beyond documented RECIST progressive disease per Investigator's judgment
  - Added definition of Phase II Group 3
  - Revised sample size of Phase II Group 2
- Figure 4-1 Study design
  - Revised the study flow chart to reflect the introduction of the Phase II Group 3
- Section 4-2 Timing of interim analyses and design adaptation
  - Added the interim analysis on Phase II Group 3
- Section 5-1 Patient population
  - Added definition of Phase II Group 3
- Section 5-2 Inclusion criteria
  - Revised ECOG performance status to ≤1.
  - Revised criterion on biopsy requirements at baseline
  - Added specific criterion for Phase II Group 3 detailing the conditions of prior lines of treatment before study entry
- Section 5-3 Exclusion criteria
  - Added specific criterion for Phase II Group 3 detailing the restriction of prior antineoplastic treatment lines
  - Removed the exclusion criterion on fasting plasma glucose and proton pump inhibitors use.
- Section 6.1.1 Dosing regimen
  - Added the recommended phase 2 dose for the Phase II part of the trial.
- Section 6.1.2 Treatment duration
  - Added note to allow for continuation of study drugs beyond documented RECIST progressive disease per Investigator's judgment
- Section 6.2 Dose escalation guidelines for the Phase I part

  - Updated title
- Table 6-1 Dose and treatment schedule
  - Added INC280 150 mg tablet dose strength
- Table 6-4 Criteria for defining dose-limiting toxicities in the Phase I part
  - Updated title
- Section 6-3 Dose modification for toxicities
  - Updated title
- Section 6.3.1 Dose modification and dose interruption
  - Added table with recommended dose reduction steps in the Phase II part of the trial
- Table 6-11 Management of dose modification for maculopapular rashes
  - Clarified recommended clinical reassessment frequency every week
  - Added footnote clarifying the conditions for study drugs re-introduction
- Table 6-12 Management of dose modification for other rashes
  - Clarified recommended clinical reassessment frequency every 2 weeks
- Section 6.4.2 Permitted concomitant therapy requiring caution and/or action
  - Updated INC280 potency for enzymes inhibition
  - Removed statement on short acting gastric acid modulators
- Section 6.4.3 Prohibited concomitant therapy
  - Removed restriction on proton pump inhibitors
- Section 6.5.2 Treatment assignment
  - Added Phase II Group 3
- Section 6.6.1 Study drug packaging and labeling
  - Added INC280 150 mg dose strength
- Section 7.1 Study flow and visit schedule
  - Clarified that the +3 days visit window around C2D1 applies to the Phase I part of the trial
- Table 7-1 Visit evaluation schedule
  - Updated Biomarkers sections according to the main changes provided in the protocol
- Section 7.1.1 Molecular pre-screening
  - Updated to reflect the new group added in the Phase II part
  - Added a note to allow for the use of Novartis designated central laboratory results obtained as part of pre-screening in other Novartis sponsored studies
- Section 7.2.1 Efficacy assessments
  - Added collection of imaging data for potential retrospective imaging data reading for patients enrolled in cohorts using the RP2D in the Phase I part of the trial
- Section 7.2.2.5 Laboratory evaluations
  - Clarified the conditions for local laboratory results data collection in the eCRF in the Phase II part of the trial

- Section 7.2.4.1 Biomarker Assessments in Tumor
  - Added wording to allow for collection of additional optional samples
- Table 7-6 Local 12-lead ECG collection plan
  - Clarified the timeframe for ECG realization the days of PK sampling
- Table 7-8 Schedule of blood sample collections for INC280, EGF816 and LMI258 PK assessment during Phase II part (first 10 patients dosed)
  - Added missing dose reference numbers
- Table 7-9 Schedule of blood sample collections for INC280, EGF816 and LMI258 PK assessment during Phase II part (rest of patients)
  - Added missing dose reference numbers
- Section 7.2.4.1 Biomarker assessments in tumor
  - Updated to clarify the samples requirements in the Phase I and in the Phase II
- Section 7.2.4.2 Assessment of c-MET and EGFR status in cfDNA samples
  - Added additional time-points for blood sample collection during the course of the study.
- Table 7-10 Biomarker collection plan in the Phase Ib part
  - Updated the table presentation and wording on optional sample collection
- Table 7-11 Biomarker collection plan in the Phase II part
  - Created to detail the tumor samples requirements in the expansion phase
- Section 8.5 Data Monitoring Committee
  - Added rationale for the absence of DMC in the Phase II part of the trial
- Section 10 Statistical methods and data analysis
  - Added conditions for primary analysis achievement
  - Clarified the primary objective and the primary variable of the Phase II analysis
  - The analysis methodology for the Phase II Group 1 was revised by introducing a separate estimation of the ORR for patients with T790M mutation and without
  - Changed the planned analysis of Phase II Group 2 to descriptive because of the reduced sample size in this group
  - Introduced Phase II Group 3 in the primary endpoint definition and specified the analysis
  - Clarified the analysis of adverse events and replaced so-called safety event categories by adverse events of special interest
  - Provided more details for the secondary efficacy endpoint section and added time to response
  - Added interim analysis methodology and the stopping rule for Phase II Group 3
  - Modified the operating characteristics for the Phase II Group 1 based on the changed analysis and added operating characteristics for Phase II Group 3
- Table 10-1 Noncompartmental pharmacokinetic parameters
  - Corrected the definition of accumulation ratio

- Section 13 References
  - Added two references
- Appendix 3 - Permitted concomitant medications requiring caution
  - Removed H2 receptor antagonist
- Appendix 4 - Prohibited concomitant medications
  - Removed proton pump inhibitors restriction

IRB/IEC/REB Approval

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 04

Amendment rationale

As of 21-Sep-2015, 15 patients have been enrolled in the Phase Ib part (dose-escalation) of the study at 7 sites in 6 countries in Asia, Europe and Canada.

The main purpose of this amendment is to implement a centralization of analysis for the resistance mutations $EGFR^{T790M}$ and c-MET oncogene amplification at a Novartis designated central laboratory for all patients entering into Phase II, in order to simplify the overall study logistics, and improve the quality and robustness of the resistance mechanisms data and analyses through use of uniform testing methods with controlled reproducibility and repeatability characteristics.

Furthermore, Amendment 4 implements other changes as follows:

- The 50 mg dose strength of EGF816 tablets is being introduced, which will decrease the number of tablets to be administered potentially allowing for better compliance and comfort of patients.
- In order to optimize the patient safety and the toxicity monitoring as well as to align Novartis study protocols, the QTcF eligibility criterion and the management guidelines for pancreatic toxicity have been revised. Therefore, the exclusion criterion for QTcF has been updated implementing specific QTcF requirements for male and female patients respectively. The exclusion criteria, the corresponding Dose-limiting toxicity definition and the list of prohibited concomitant medications with known QTcF prolongation effect are also being updated accordingly for consistency with other Novartis Oncology sponsored studies. The amendment also provides the investigators with modified dose modification rules for pancreatic toxicity.
- Exclusion criteria for patients with out of range laboratory values and for contraception use are being updated for consistency with other Novartis Oncology sponsored studies. The Note for exceptions to prior anti-cancer therapies is being removed for the same reason.
- Of note, the changes in selection criteria provided in this amendment have very little impact on the level of heterogeneity among studies used for deriving priors for the Bayesian Logistic Regression Model. Therefore, the same priors for the model parameters can be used in analyzing the data from the updated population. In addition, the dose-DLT data observed in this study thus far are still valid according to the refined population and DLT criteria.
- The definition of the end of study is being updated to detail study continuation conditions after completion of the primary analysis until all patients are discontinued, or until another clinical trial becomes available for all ongoing patients to be transferred to that clinical study and continue to receive INC280 + EGF816.
- Serious Adverse Event reporting process is being updated to allow for possible electronic reporting to the Sponsor, and for consistency with other Novartis Oncology sponsored studies.
- The possibility of using bisphosphonates during the study is being clarified.
- The use of an Interactive Response Technology system in the Phase II part of the study is being detailed to specify the enrollment and the study drug dispensation tracking via the

application. The time-points for IRT registration by study site personnel are also being detailed.

- Modalities and conditions for patient re-screening after screen failure are being introduced, together with screening assessments to be performed again during the new screening phase.
- The glossary of terms is being updated for consistency with the CRF Completion Guidelines document.
- The time-points for PFS rate analysis are being updated for consistency with visit evaluation schedule.

Changes to the protocol:

- List of abbreviations:
  - Added eSAE, NTI
- Glossary of Terms:
  - Added definition of Adjuvant chemotherapy, Neoadjuvant chemotherapy, Palliative care, Therapeutic setting, Treatment line (regimen)
- Protocol summary:
  - Added definition of Phase II Group 1 and Phase II Group 2
  - Updated selection criteria
- Section 4.1 Description of study design
  - Added centralization of resistance mechanisms testing in the Phase II part of the study
  - Corrected typo
- Section 4.3 Definition of End of Study
  - Added conditions of study continuation after primary analysis completion
  - Updated circumstances of end of study
- Section 5.2 Inclusion criteria
  - Updated criterion on molecular testing requirements to reflect the centralization of resistance mechanisms analyses in the Phase II part of the study
  - Revised list of prior EGFR-TKI therapies for Phase II patients for consistency with Phase Ib patients
- Section 5.3 Exclusion criteria
  - Corrected typo on HGF targeting therapy
  - Removed Note for exceptions to prior anti-cancer therapies
  - Added detailed criterion on cardiac repolarization abnormalities
  - Revised abnormal laboratory value thresholds for platelets, glucose, serum creatinine
  - Added method of calculation for creatinine clearance
  - Updated list of highly effective contraceptive methods
- Section 6.1.1 Dosing regimen
  - Added 50 mg EGF816 tablets dose strength
- Section 6.2.1 Starting dose

  - Corrected typo in rationale
  - Table 6-4 Criteria for defining Dose Limiting Toxicities: updated pancreatic toxicities according to revised dose adjustment recommendations in case of amylase and lipase elevations. Corrected typo.
- Table 6-5 Criteria for interruption and re-initiation of EGF816 and INC280
  - Updated amylase/lipase dose adjustments. Corrected typo.
  - Added reference to new protocol section on follow-up for potential QTcF prolongation events.
- Section 6.3.4.1 Follow up on potential QTcF prolongation is being added
- Section 6.3.4.2 Follow up for potential drug-induced liver injury (DILI) cases: corrected typo
- Section 6.4.1 Permitted concomitant therapy
  - Added possibility of use of bisphosphonates during the study
- Section 6.4.3 Prohibited concomitant therapy
  - Added medications with known risk of QT interval prolongation and/or known risk to cause Torsades de Pointe
- Section 6.5.1 Patient numbering
  - Added IRT registration time-points
- Section 6.5.2 Treatment assignment
  - Added functionality of IRT for group allocation and study drug dispensation
- Section 6.6.1 Study drug packaging and labeling
  - Added 50 mg EGF816 tablets dose strength
- Table 7-1 Visit evaluation schedule
  - Corrected typo
  - Added IRT registration time-points
  - Updated molecular pre-screening requirements to reflect the centralization of resistance mechanisms analyses in the Phase II part of the study.
- Section 7.1.1 Molecular pre-screening
  - Updated molecular pre-screening requirements to reflect the centralization of resistance mechanisms analyses in the Phase II part of the study.
- Section 7.1.2 Screening
  - Added modalities and conditions for re-screening
- Section 7.2.4 Biomarkers and Table 7-9 Biomarker sample collection plan
  - Updated molecular pre-screening requirements to reflect the centralization of resistance mechanisms analyses in the Phase II part of the study.
- Section 8.1 Adverse events
  - Added collection of CTCAE Grade 5 events as a seriousness criterion
- Section 8.2 Serious Adverse Events
  - Revised process for initial SAE reporting and follow-up information submission.

- Section 10.5.2 efficacy objectives
  - Updated PFS rate analysis time-points
- Appendix 4 Prohibited concomitant medications
  - Added medications with known risk of QT interval prolongation and/or known risk to cause Torsades de Pointe

IRB/IEC/REB Approval

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 03

Amendment rationale

As of 11-Aug-2015, 14 patients have been enrolled in the Phase Ib part (dose-escalation) of the study at 7 sites in 6 countries in Asia, Europe and Canada.

The main purpose of this amendment is to provide detailed information about an Urgent Safety Measure related to EGF816. As of 08-July-2015, 2 serious adverse events (SAEs) of viral hepatitis B (HBV) reactivation have been reported in 2 patients participating in the CEGF816X2101 study (A phase I/II, multicenter, open-label study of EGF816, administered orally as single-agent in adult patients with EGFRmut solid malignancies). One case had a fatal outcome, and the second case was medically significant. The fatal case concerned a patient who received EGF816 capsules at a dose of 225 mg QD, had HBV infection in the past, and was not on antiviral treatment at study entry. The patient developed a HBV reactivation 7 months after EGF816 initiation and died due to hepatic failure despite initiation of antiviral treatment after HBV reactivation was confirmed. The second patient also received EGF816 capsules at a dose of 225 mg QD, had a history of chronic HBV diagnosed on an unknown date, and was not on antiviral treatment at the time of study entry. HBV reactivation was detected in this patient while approximately 10 weeks on study. Antiviral treatment was immediately initiated, EGF816 was interrupted, and the HBV infection was brought under control. The patient later resumed EGF816 at the same dose of 225 mg QD. The viral reactivation in these two patients was likely due to immunosuppression related to EGF816. Reactivation of HBV and viral hepatitis C (HCV) has been reported with other anticancer therapies that suppress the immune system. To ensure the safety of all patients participating in the CINC280X2105C trial, changes have been made to the protocol to implement safety measures regarding the reactivation of HBV and HCV.

As a consequence, the following eligibility criteria were revised:

- To exclude patients with other malignancies, who underwent a bone marrow or solid organ transplant, with a known history of human immunodeficiency virus infection, or receiving immunosuppressive agents or chronic corticosteroids at study entry;
- To allow patients with either HBsAg positive or HBV-DNA positive to enroll into the study if willing to take antiviral therapy1-2 weeks prior to first dose of study treatment and continue antiviral therapy for at least 4 weeks after the last dose of study treatment;
- To allow new patients with negative hepatitis C antibody (HC Ab) or who are HC Ab positive but with an undetectable level of HCV-RNA into the study. Patients with detectable HCV-RNA are not eligible to enroll into the study.

Of note, the changes in selection criteria provided in this amendment do not affect the heterogeneity among studies used in the model. In addition, the dose-DLT data observed in this study thus far are still valid according to the refined population.

Finally, a recommendation of skin biopsy in case of maculopapular rash was added to the guideline for the management of skin-related toxicities that was introduced in Amendment 02. The purpose of this recommendation is to further investigate the pathophysiological mechanism related to the adverse event.

Changes to the protocol:

- Updated Section 1.2.2 Overview of EGF816:
  - Updated Section 1.2.2.1.1 Non-clinical pharmacokinetics based on most recent available data.
  - Updated Section 1.2.2.1.3 Nonclinical toxicology summary to include preclinical results showing inhibition of TEC family kinases by EGF816 and their potential role in EGF816 effects.
  - Updated Section 1.2.2.2 Clinical experience with information on the 2 SAEs of the HBV reactivation in patients participating in CEGF816X2101. Updated preliminary efficacy and safety results based on currently available data.
- Section 5.2 Inclusion criteria:
  - Added a criterion to allow new patients with either HBsAg positive or HBV-DNA positive to enroll into the study if willing to take antiviral therapy 1-2 weeks prior to 1st dose of EGF816 treatment and continue on antiviral therapy for at least 4 weeks after the last dose of EGF816.
  - Added a criterion to allow new patients with negative hepatitis C antibody (HC Ab) or are HC Ab positive but with an undetectable level of HCV-RNA into the study. Patients with detectable HCV-RNA are not eligible to enroll into the study.
- Section 5.3 Exclusion criteria:
  - Added a criterion related to exclusion of other malignancies.
  - Added a criterion to exclude patients who have undergone a bone marrow or solid organ transplant.
  - Added a criterion related to exclusion of human immunodeficiency virus (HIV) seropositivity.
  - Added a criterion to exclude patients receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry.
  - Corrected the exception of criterion 15 instead of 10 (due to new criteria previously added)
- Updated Table 6-5 Criteria for interruption and re-initiation of EGF816 and INC280 to include hepatitis B and C testing as applicable in case of hepatotoxicity, and to include recommendations in case of HBV or HCV reactivation.
- Added Section 6.3.2 Guidelines for screening, monitoring and management of HBV and HCV reactivation.
- Added Table 6-6 to summarize actions to be taken based on hepatitis B screening results.
- Added Table 6-7 to summarize guidelines for management of HBV reactivation.
- Added Table 6-8 to summarize guidelines for management of HCV reactivation.
- Renumbered Tables 6-6, 6-7 and 6-8 in Amendment 02 to Tables 6-9, 6-10 and 6-11 due to the insertion of Section 6.3.2
- Updated Table 6-11 to recommend consideration of skin biopsy in the event of a maculopapular rash.

- Updated Sections 6.4.2 and 6.4.3 to include additional permitted concomitant therapies requiring caution and/or action, and additional prohibited concomitant medications.
- Updated Table 7-1 Visit evaluation schedule to include hepatitis B and C screening and monitoring
- Updated Section 7.1.2 Screening to detail hepatitis B and C requirements before study treatment initiation.
- Updated Section 7.1.2.2 Patient demographics and other baseline characteristics to include HBV and HCV status collection within patient characteristics data.
- Updated Section 7.2.2.5 Laboratory evaluation and Table 7-4 Central/local clinical laboratory parameters collection plan to include hepatitis B and C testing at screening and as applicable during the study conduct.
- Added Section 7.2.2.5.5 HBV and HCV testing to list viral serology investigations within mandatory laboratory evaluations.
- Updated Table 14-15 Prohibited concomitant medications in Section 14.4 Appendix 4 based on last update from the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: Apr-2015)

Amendment 02

Amendment rationale

As of 29-Jun-2015, nine patients have been enrolled in the Phase Ib part of the study (dose-escalation) from 4 sites in 4 countries.

The main purpose of this amendment is to introduce a formulation change for EGF816 from capsules to tablets (viable formulation for commercialization).

During the course of the trial, parallel safety cohorts with tablets will be introduced to describe the pharmacokinetic properties of the combination with the new formulation, and to confirm or declare the MTD/RP2D of the combination with the new formulation.

Furthermore, Amendment 2 implements other important changes as follows:

Rationale for the update related to EGF816 safety:

Because rash, particularly maculopapular rash or rash pruritic, is an adverse event frequently observed following treatment with EGF816, recommended guidelines for management and dose modification of rash/skin toxicities were provided.

In addition, EGF816 program level updates were made in the clinical overview section.

Rationale for the update related to INC280 safety:

Concurrent elevation of ALT and/or AST and total bilirubin: After 28-Sep-2014 (cut-off date of the current [Investigator's Brochure], a female patient experienced a serious, unexpected, possibly related adverse event of abnormal liver function tests during treatment with a combination of INC280 and gefitinib while enrolled in the study [CINC280X2202]. The investigator assessed the adverse event suspected to be related to the combination of INC280 and gefitinib. This adverse event met the lab criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination.

The protocol is therefore being amended to update the dose modifications guideline for hepatotoxicity in regard to discontinuing study medication(s) with concurrent elevation of ALT and/or AST >3×ULN and total bilirubin >2×ULN with ALP <2×ULN, in the absence of signs of cholestasis, hemolysis, and alternative causes of the liver injury (e.g., concomitant use of hepatotoxic drug(s), alcoholic hepatitis, etc.). Specific work-up for potential Hy's law cases has been added to the protocol. The dose modification rules and the dose limiting toxicity for liver toxicity as well as the follow-up evaluations for hepatic toxicities have also been updated accordingly.

Photosensitization: Based on the preclinical data which suggests photosensitization potential of INC280, precautionary measures against ultraviolet exposure are being included in the protocol in addition to the information provided in the Investigator's Brochure.

In addition, the clinical overview of INC280 was updated based on the Investigator's Brochure last update (current version is now 5.2 with cut-off date 28-Sep-2014).

Rationale for the changes in eligibility criteria:

- Update of exclusion criteria
  - EGFR TKIs to be taken into consideration as prior lines of treatment were specified in exclusion criterion 1.
  - To allow patients with controlled brain metastasis to enter the trial, the exclusion criterion 6 was modified.
  - Parameters and conditions were included in exclusion criterion 8 to better define patients with uncontrolled cardiovascular disease,
  - To reduce the washout period from 4 weeks to 2 weeks for patients who received radiotherapy for all other localizations than lung or whole brain, or in case of palliative radiotherapy, the exclusion criterion 12 was modified.
  - To exclude patients with relevant elevations for glucose and alkaline phosphatase, out of range laboratory values for these parameters were included to exclusion criterion 15. In addition, electrolytes (potassium, magnesium, phosphorus, total calcium (corrected for serum albumin)) are added to be within normal ranges or corrected during the screening period.
  - The exclusion criterion 21 for the contraception period after study treatment discontinuation was updated from 7 days to 3 months based on currently available pharmacokinetics data for EGF816.
- Addition of exclusion criteria:
  - To exclude patients with interstitial lung disease to reflect the potential class effect of EGFR TKIs observed for first and second generation EGFR TKIs.
  - To ensure adequate drug absorption, patients with significant gastro-intestinal (GI) function impairment were excluded;

To exclude patients who have not recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v 4.03);Rationale for the update related to molecular screening:

- Eligibility criteria for defining c-MET dysregulation have been refined based on experience with individuals enrolled in other INC280 studies in the EGFR TKI resistant setting e.g. [CINC280X2202]. The study will focus on the high c-MET dysregulation cohort defined as either a gene amplification (GCN≥4) and those with IHC 3+ overexpression. The recent publication by Schildhaus et al suggests that, in NSCLC, the use of GCN rather than gene ratio by FISH is better able to define amplified patients based on the biology of the amplicon. Therefore we removed the reference to ratio as a way of defining amplification. Finally the GCN determining enrollment is modified to 4 copies to enable a greater clarity on the cut-off for amplification to determine patients most likely to respond to the combination of EGF816 with INC280.
- To better define the patient population, the mutational status pre-requirements for Phase Ib and Phase II Group 1 were updated to clarify that EGFR mutation L858R and/or ex19del need to be locally documented, and updated for Phase II Group 2 because de novo EGFRT790M mutation may occur without the presence of EGFR mutation L858R and/or ex19del. In addition, local analytical method characteristics for acceptable T790M mutational status testing were updated.

Rationale for the update on concomitant therapies:

- To allow bone palliative radiation therapy throughout the study, permitted concomitant therapies were updated, and anticoagulation treatment was permitted if INR has been established within the therapeutic range prior to study entry.
- Further updates were made on concomitant therapies based on current EGF816 pharmacological data. Potential for Drug-Drug Interactions with EGF816 metabolite LMI258 was removed due to low plasma content of LMI258 obtained in this study as well as with single agent treatment in CEGF816X2101 study.

Rationale for the update of criteria for interruption and re-initiation of EGF816 and INC280:

- Because of the Hy`s law case observed in the CINC280X2202 study, the criteria were modified for hepatotoxicity.
- Because of the skin related toxicity observed for EGF816, an additional table for the management of this toxicity was added.
- Given the early stage of drug development for EGF816, more detailed guidance was provided on the criteria for QTc prolongation, vomiting, diarrhea and nausea.

Operational updates:

- To implement an Interactive Response Technology (IRT) in the Phase II part of the study to track patient enrollment, allocate patients into the sub-groups based on their disease characteristics at study entry, and track EGF816 and INC280 drug dispensing.
- To implement central laboratories to evaluate the safety of INC280 and EGF816 (e.g., hematology, chemistry, coagulation and pregnancy test) in the Phase II. The use of a central laboratory will allow a consistent laboratory assessment and interpretation of the results across a multitude of countries participating in this study.
- To collect CT/MRI scans for potential central blinded review.
- To implement the Discontinuation of Clinical Trial Protocol Elements (DOCE) language to provide guidance on how to effectively manage patients who discontinue certain Clinical Trial Protocol elements, those who withdraw consent, and those who are lost to follow-up.
- To clarify the biomarker collection and analysis plan:
- Update of molecular pre-screening consent process to have all patients sign the document.
- Update of the biomarker collection plan to clarify the study requirements in terms of activating mutations testing and resistance mechanisms testing at prescreening.

[redacted]

- Addition of sensitivity and resistance mechanisms studies. The purpose of these optional studies is to help understand the molecular pathways associated with sensitivity or resistance to INC280 therapy.

Rationale for other updates:

The hypothetical dose-escalation scenarios presented in Appendix 2 of the protocol were updated based on the currently available data in INC280 and EGF816 single-agent studies used in the model.

Of note, the changes in selection criteria provided in this amendment do not affect the heterogeneity among studies used in the model. In addition, the dose-DLT data observed in this study thus far are still valid according to the refined population, together with the new hepatic DLT definition (no cases observed within patients enrolled with the previous version of the protocol). Therefore, the selection criteria update and the DLT definition update do not affect the BLRM results.

Changes to the protocol

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

List of abbreviations

- Added ADME, ALP, BAL, BID, cfDNA, DBP, DOCE, FISH, FU, GCP, GCN, GGT, GI, IC50, IHC, IRT, LFT, mut, NGS, NOAEL, NRU, PTT, QTcF, SBP, UV definition

Glossary list

- Added/removed and amended definitions.

Section 1.2.1 Overview of INC280

- Amended presentation of INC280 based on the data from 28-Sep-2014 (data cut-off date for Investigator's Brochure update)

Section 1.2.1.1 Non-clinical experience

- Added potential for photosensitization for INC280 observed in in vitro assays.

Section 1.2.1.2 Clinical experience

- Added the efficacy and safety summaries of INC280 based on the data from 28-Sep-2014 (data cut-off date for Investigator's Brochure update) and the data from 30-Jan-2015 for study [redacted].

Section 1.2.2.2 Clinical experience

- Added the efficacy and safety summaries of EGF816 based on the data from 02-Feb-2015 in CEGF816X2101 study.
- Added Figure 1-1 to provide EGF816 clinical activity observed at all dose levels tested.

Section 4.1 Description of study design

- Revised the definition of activating and resistance EGFR mutations. Revised the definition of c-MET dysregulation.
- Removed EGFR L858R or ex19del for Phase II Group 2 in Figure 4-1.
- Revised molecular pre-screening requirements.

- Removed requirement for archival or newly obtained tumor biopsy sample submission to central lab at baseline.

Section 4.4 Early study termination

- Updated language for patient withdrawal.

Section 5.1 Patient population

- Revised mutation status pre-requirements for Phase Ib and Phase II Group 1, and for Phase II Group 2.

Section 5.2 Inclusion criteria

- Revised baseline EGFR mutation characteristics, and local results or biopsy collection requirements.
- Removed mandatory requirement for archival tumor from prior to previous EGFR TKI treatment submission.

Section 5.3 Exclusion criteria

- Added EGFR-TKIs to be taken into consideration as prior lines of treatment.
- Added exception to one previous treatment line with an approved EGFR-TKI to allow study entry in case of EGFR-TKI discontinuation due to adverse event.
- Added exception to patient with controlled brain metastases to participate in the trial.
- Updated exclusion criterion in case of uncontrolled cardiovascular disease.
- Updated exclusion criterion in case of out of range laboratory values.
- Added exclusion criterion for patients with abnormal potassium, magnesium, phosphore, total calcium laboratory values.
- Added exclusion criterion in case of history or presence of interstitial lung disease.
- Added exclusion criterion for patients who have not recovered from all prior anticancer therapies related toxicities to grade ≤ 1 (CTCAE v 4.03).
- Added exclusion criterion for patients with impairment of GI function.
- Removed specific bilirubin abnormal value for Gilbert's syndrome patients.
- Removed definition of pregnancy for pregnant women exclusion criterion.
- Revised the contraception period after study treatment discontinuation from 7 days to 3 months.

Table 6-1 Dose and treatment schedule

- Added EGF816 Tablets.
- Added footnote to clarify that "additional dose strengths might be added".

Section 6.1.1 Dosing regimen

- Added the word tablet where previously only EGF816 capsules were mentioned.
- Added pomegranate and juice within list of fruits that should be avoided during the study treatment period.
- Added precautionary measures regarding ultraviolet exposure.

Section 6.2.1 Starting dose rationale

- Added starting dose rationale for the formulation change from EGF816 capsules to tablets.

Table 6-2 Provisional dose levels for EGF816

- Specified that starting dose applies for EGF816 capsule formulation.

Table 6-3 Provisional dose levels for INC280

- Specified that starting dose applies for EGF816 capsule formulation. Section 6.2.3 Guidelines for dose escalation and determination of MTD/RP2D
- Added consequences of EGF816 formulation change on BLRM and cohorts implementation in the dose-escalation phase of the study.

Table 6-4 Criteria for dose-limiting toxicities

- Clarified that AST or ALT = grade 3 and skin and subcutaneous disorders = grade 3 have to be observed during > 7 consecutive days.
- Revised the definition of AST and/or ALT > grade 3 and > grade 2 total bilirubin and ALP < 2 x ULN to meet Hy's Law case definition.

Table 6-5 Criteria for interruption and re-initiation of EGF816 and INC280

- Revised guidance for hepatic investigations dose modification recommendations.
- Added guidance for discontinuation based on definition of Hy's Law.
- Revised cardiac investigations definition.
- Revised gastro-intestinal disorders definition.
- Removed rash/photosensitivity recommended dose modifications.
- Removed respiratory recommended dose modifications.
- Added LFTs definition in footnote.

Section 6.3.2 Guidelines for the management and dose modification of skin related toxicities

- Added new section on guidelines for prevention and symptomatic care of rash/skin toxicities, and management and dose modification for maculopapular rash and other rashes.

Section 6.3.3 Follow-up for toxicities

- Revised requirements and duration for follow-up for Drug-Induced Liver Injury.

Section 6.4.1 Permitted concomitant therapy

- Added palliative bone radiation and anticoagulation treatment.

Section 6.4.2 Permitted concomitant therapy requiring caution and/or action

- Removed EGF816 effect on CYP2D6 and CYP2C8.
- Added EGF816 and P-gp interaction.

Section 6.5 Patient numbering, treatment assignment

- Added that IRT will be used for Phase II patients.

Section 6.5.1 Patient numbering

- Added paragraph on IRT use for Phase II patients.

Section 6.6.1 Study drug packaging and labeling

- Added label information for IRT use with Phase II patients.

- Added word ‘tablet’ throughout the text where previously only EGF816 capsules were mentioned.
- Added packaging details for EGF816 tablets.

Section 7.1 Study flow and visit schedule

- Clarified duration of Cycle 1 visit windows.

Table 7-1 Visit evaluation schedule

- Added IRT registration.
- Added headers for assessment sub-types.
- Added assessments for optional whole blood sample.
- Revised biomarkers assessment definition.
- Added blood sample collection for c-MET and EGFR status determination in cfDNA.
- Revised footnotes related to biomarker assessments.
- Addition of optional study on sensitivity and resistance mechanisms to INC280

Section 7.1.1 Molecular pre-screening

- Revised activating and resistance mutational status pre-requirements.
- Added local analytical method characteristics for acceptable T790M mutational status testing.
- Revised c-MET dysregulation definition.
- Changed Phase II Group 2 screening requirements.
- Replaced IHC with FISH as main method of c-MET expression analysis.
- Section 7.1.2 Screening Removed requirement for archival or newly obtained tumor biopsy sample submission to central lab at baseline.
- Defined the duration of the screening period.

Section 7.1.4 Discontinuation of Study Treatment

- Updated information in line with new patient withdrawal language.
- Added the duration of maximum study drug interruption authorized as per protocol.
- Added that study drug discontinuation has to be recorded in the IRT.
- Removed Section 7.1.4.1 Criteria for premature patient withdrawal.

Section 7.1.5 Withdrawal of consent

- Added new section in line with new language for withdrawal of consent.

Section 7.1.6 Follow-up for safety evaluations

- Amended section title.
- Updated section in line with new language for withdrawal of consent.

Section 7.1.7 Lost to follow-up

- Added new section in line with new language for withdrawal of consent.

Section 7.2.1 Efficacy assessments

- Added collection of imaging data for potential blinded central review.

Section 7.2.2.5 Laboratory evaluations

- Added centralization of laboratory parameters assessment for safety purposes.

Section 7.2.2.6 Cardiac assessments

- Added triplicate ECGs at all time-points during the trial.

[redacted]

Section 8.2.2 Reporting

- Clarified follow-up for SAEs related to biopsy procedures.

Section 9.3 Data collection

- Added details for IRT data collection.

Section 9.4 Database management and quality control

- Added details for IRT data collection.

Section 10.4.2.1 Phase Ib

- Added paragraphs under the title "Starting dose combination using the tablet formulation of EGF816" on new BLRM for tablet formulation of EGF816.

Section 13 References

- Updated the list of references based on clinical overview updates.

Section 14.2 - Appendix 2

- Updated title of appendix to "Appendix 2 – Prior derivation for the Bayesian logistic regression model and hypothetical dose escalation scenarios".

Section 14.2.2.4 Summary of the distribution of DLT rate

- Updated title to "Summary of the distribution of DLT rate".
- Updated values in Table 14-11. An error in the Bayesian model has been corrected in this version and the model is re-run to get the updated values.

Section 14.2.3 Methodology for down-weighting

- Previously Section 14.2.3. This section has been moved ahead of "Prior Specification" section.
- Added new paragraph for new formulation of EGF816.

Table 14-11 Levels of heterogeneity for historical data from different studies and for co-data

- Added new table.

Table 14-12 Hypothetical dose escalation scenarios

- Updated table number and title. Updated dose-escalation scenarios related probabilities.

Section 14.2.5 Starting dose of the EGF816 tablet

- Added section on starting dose including new table "Table 14-13 Available dose-DLT data from single-agent studies as of Feb 2015".

- Removed statement that the outputs from the BLRM (mainly the summary of the distribution of DLT rates at different dose levels) will be summarized in a separate document. This statement was initially intended for internal documentation only.

Section 14.3 Appendix 3 - Permitted concomitant medications requiring caution

- Removed CYP2C8 or CYP2D6 sensitive substrate category.
- Updated with current information for concomitant medications used with caution.

Section 14.4 Appendix 4 - Prohibited concomitant medications

- Removed CYP2D6 substrate with NTI category.
- Updated with current information for concomitant medications prohibited.

IRB/IEC/REB Approval

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 01

Amendment rationale

This amendment addresses the following revisions suggested by a regulatory authority:

- To reduce EGF816 starting dose to 50 mg qd,
- To clarify the subsequent escalation of EGF816 and INC280 doses and
- To revise the DLT definitions by adding Grade 2 pneumonitis as dose-limiting toxicity.
- To provide the latest available clinical safety and PK data for EGF816 and INC280 tablet formulation
- To provide updated hypothetical scenarios in reflection of the reduced starting dose of EGF816 and the updated priors based on the updated safety information.

Additional changes for clarification were also made (please see below Changes to the protocol for details).

Changes to the protocol

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

Section 1.2.1.2.1 Clinical safety

- Addition of safety data of INC280 tablet

Section 1.2.1.2.2 Clinical pharmacokinetics

- Addition of pharmacokinetic data of INC280 tablet

Section 1.2.2.2 Clinical experience

- Addition of safety data of EGF816

Section 2.3 Rational for dose and regimen selection

- Reduction of EGF816 starting dose
- Deletion of wording regarding adjustment of starting doses prior to enrollment of patients in the trial

Section 4.1 Description of study design

- Correction of the number of patients to be enrolled in Phase II Group 2 to N=20 in Figure 4-1 Study design

Section 5.3 Exclusion criteria

- Correction of a typographical error in exclusion criterion #4

Section 6.1.1 Dosing regimen

- Reduction of EGF816 starting dose
- Deletion of wording regarding adjustment of starting doses prior to enrollment of patients in the trial
- Deletion of “Patients will consume another glass of water approximately two hours after each dosing” as this is not applicable to INC280 tablets and EGF816.

Section 6.2.1 Starting dose rationale

- Reduction of EGF816 starting dose
- Deletion of wording regarding adjustment of starting doses prior to enrollment of patients in the trial

Section 6.2.2 Provisional dose levels

- Split Table 6-2 Provisional dose levels for EGF816 and INC280 into two tables (Table 6-2 provisional dose levels for EGF816 and Table 6-3 provisional dose levels for INC280)
- Reduction of EGF816 starting dose
- Revision of EGF816 provisional dose levels

Section 6.2.3.2 Dose cohort modification

- Reduction of EGF816 starting dose
- Deletion of wording regarding adjustment of starting doses prior to enrollment of patients in the trial

Section 6.2.4 Definitions of dose limiting toxicities

- Addition of Grade 2 pneumonitis as DLT in Table 6-4 (Table 6-3 in original protocol version)– Criteria for defining dose-limiting toxicities

Section 6.3.1. Dose modification and dose interruption

- Addition of criteria for dose modification for pneumonitis in Table 6-5 (Table 6-4 in original protocol version) Criteria for interruption and re-initiation of EGF816 and INC280 treatment.
- Clarification of diarrhea grade 2 dose modification recommendation in Table 6-5 to maintain INC280 dose level if diarrhea returns as grade 2 and resolves to ≤ grade 1

Section 7 Study flow and visit schedule

- Formatting correction of Table 7-1 Visit evaluation schedule to have prior/concomitant medication information collected at Cycle 1 Day 1

Section 8.1.1

1. “Delete for NOVDD Trials as outcome is not collected” has been deleted as it is instruction text from the Novartis protocol template which should not appear in the final version of the protocol.

Section 10.1.5 Pharmacokinetic analysis set

- Deletion of repeated text “patients will be removed from the determination of individual INC280, EGF816 or LMI258 PK parameters on case by case basis.”

Section 14.2 Appendix 2- Operating characteristics of the Bayesian logistic regression mode and hypothetical dose escalation scenarios

- Addition of newly available dose-DLT data on EGF816 and INC280 from the single agent studies to update the distribution of DLT rates
- Modification of the hypothetical dose escalation scenarios in Table 14-11 using the newly available single agent and the new starting dose combination.

IRB/IEC/REB Approval

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Protocol summary

Protocol number	CINC280X2105C
Title	A phase Ib/II, multicenter, open-label study of EGF816 in combination with INC280 in adult patients with EGFR mutated non-small cell lung cancer
Brief title	Study of safety and efficacy of EGF816 in combination with INC280 in non-small cell lung cancer patients with EGFR mutation
Sponsor and Clinical Phase	Novartis Phase Ib/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of nazartinib in combination with capmatinib and to estimate the preliminary anti-tumor activity of nazartinib in combination with capmatinib in participants with advanced non-small cell lung cancer with documented EGFR mutation. To explore the hypothesis that targeting the two main EGFR resistance mechanisms, acquisition of T790M and MET dysregulation, may prevent or overcome the acquired resistance to EGFR TKIs, by combining the third generation EGFR TKI, nazartinib, and the highly selective and potent MET inhibitor, capmatinib, in non-small cell lung cancer participants with documented EGFR mutation who have developed resistance to EGFR TKI treatment or who never received any prior line of systemic antineoplastic therapy for advanced disease (For participants in Phase II Groups 1 to 4, antineoplastic systemic therapy administered as adjuvant or neo-adjuvant treatment more than six months prior to study enrollment is not considered a prior line of therapy for purpose of this study). To explore the hypothesis that capmatinib monotherapy is safe and beneficial to participants in EGFR mut, T790M negative, EGFR TKI resistant MET amplified NSCLC.
Primary Objective(s)	**Phase Ib part:** To estimate the MTD or RP2D of nazartinib in combination with capmatinib. **Phase II part:** To estimate the preliminary anti-tumor activity of nazartinib in combination with capmatinib (Groups 1, 2 and 3) and to characterize the safety and tolerability of nazartinib in combination with capmatinib when taken with food (Group 4). To estimate the preliminary anti-tumor activity (ORR) of capmatinib monotherapy (Group 5).
Secondary Objectives	To characterize the safety and tolerability of nazartinib in combination with capmatinib (Phase Ib/II Groups 1 to 4). To characterize the PK of nazartinib in combination with capmatinib when given in combination under fasted state or with food (Phase Ib/II Groups 1 to 4). To evaluate the preliminary anti-tumor activity of nazartinib in combination with capmatinib (Phase Ib/ Phase II Groups 1 to 4). To estimate the preliminary anti-tumor activity (DOR, DCR, and PFS) of capmatinib monotherapy (Phase II Group 5) To characterize the safety and tolerability of capmatinib monotherapy as well as capmatinib in combination with nazartinib therapy (Phase II Group 5).
Study design	This study has been designed as a Phase Ib/II, multi-center, open-label study starting with a Phase Ib dose escalation part followed by a Phase II part. At the end of the Phase Ib part, once the MTD or RP2D has been declared, additional participants with NSCLC will be enrolled in the Phase II part in order to assess the preliminary anti-tumor activity of nazartinib in combination with capmatinib. In an additional group (Phase II Group 5), preliminary anti-tumor activity will be evaluated in a two-stage design. This group will enroll 10 participants at the first stage with a futility analysis. At the second stage, additional participants will be enrolled provided that the futility analysis did not show any evidence of lack of efficacy of the capmatinib monotherapy. Participants with locally advanced or metastatic NSCLC will be assigned into different groups according to their resistance mechanisms:

	Phase II Group 1: Previously documented EGFR activating mutation Any T790M, any MET Who received 1 to 3 lines of systemic antineoplastic therapy (chemotherapy and/or targeted therapy) before study entry, including 1 line maximum of first or second generation EGFR TKI Who progressed on the prior line of first or second generation EGFR TKI **Phase II Group 2:** Documented de novo EGFR T790M mutation Who are treatment naïve or received maximum 2 lines of systemic antineoplastic therapy (chemotherapy and/or targeted therapy) prior to study entry, but no therapy known to inhibit EGFR **Phase II Group 3:** Previously documented EGFR activating mutation T790M negative, any MET Who never received any prior line of systemic antineoplastic systemic therapy (chemotherapy and/or targeted therapy) prior to study entry **Phase II Group 4:** Previously documented EGFR activating mutation Any T790M, any MET Who are treatment naïve or failed (defined as intolerance to treatment or documented disease progression) maximum 2 prior lines of any systemic antineoplastic therapy for advanced disease. Group 4 participants will take the combination therapy with food (unrestricted meal type) whilst Phase Ib and Phase II Groups 1, 2 and 3 participants take the combination therapy under fasting condition. **Phase II Group 5:** Previously documented EGFR activating mutation (e.g., L858R and/or ex19del), T790M negative, acquired MET amplification who have progressed on one prior line of therapy for advanced/metastatic NSCLC disease. Enrollment of participants who have progressed on prior line with osimertinib will be a minimum of 50% of the planned total number of participants while participants who progressed on other third generation EGFR TKI will represent a maximum of 10% of the planned total number of participants.
Population	Adult participants with non-small cell lung cancer who have EGFR mutations.
Key Inclusion criteria	• Participants (male or female) ≥ 18 years of age. • **Participants in Phase Ib and Phase II Groups 1 to 4** with histologically documented, locally advanced or recurrent (stage IIIB who are not eligible for combined modality treatment) or metastatic (Stage IV) non-small cell lung cancer. **Participants in Phase II Group 5** must have stage IIIB/IIIC (not amenable to curative surgery, chemoradiation or radiation) or stage IV NSCLC at the time of study entry according to AJCC version 8. • **Participants in Phase Ib and Phase II Ggroups 1 to 4** must have locally documented EGFR mutation L858R and/or ex19del (or other rare activating mutations that confer sensitivity to first and second generation EGFR inhibitors (e.g. L861Q, G719X, S768I), or a characterized de novo EGFRT790M mutation. Biomarker requirements for participants in **Phase II Group 5** are detailed in Inclusion criteria 15. • Presence of at least one measurable lesion according to RECIST 1.1 as per Appendix 1. • Eastern Cooperative Oncology Group (ECOG) performance status ≤1. • Participants must be screened for HBV. Participants who are either HBsAg positive or HBV-DNA positive must be willing and able to take antiviral therapy 1-2 weeks prior to first dose of study treatment (capmatinib+nazartinib) and continue on antiviral therapy for at least 4 weeks after the last dose of study treatment

	(capmatinib +nazartinib). Additional management of the participants would be provided by a physician with expertise in management of HBV, if needed. • Participants must be screened for HCV. Participants must have negative hepatitis C antibody (HCV-Ab) or positive HCV-Ab but with an undetectable level of HCV-RNA. Note: participants with detectable HCV-RNA are not eligible to enroll into the study. • **For Phase Ib:** participants must have either an acceptable local result, detailing their MET and EGFRT790M status in a biopsy collected at or post progression on the previous EGFR TKI therapy or sufficient tumor material available from a biopsy collected at or post progression on the previous EGFR-TKI therapy for central assessment of MET and EGFRT790M. **For Phase II**, participants must have sufficient material available for results from central assessment of MET and EGFRT790M. The biopsy must be collected at or post progression on last EGFR TKI treatment line for Group 1 and Group 5, at any time for Groups 2, 3 and 4 at any time (if treatment-naïve) or at/or any time after progression on last antineoplastic therapy for advanced setting (if 2/3L participants); if biopsy is not available after last treatment, the most recent available archival biopsy should be collected. • **Phase Ib only:** documented progression of disease according to RECIST 1.1 while on continuous treatment with EGFR TKI (e.g. erlotinib, gefitinib or afatinib). • **Phase II Group 1 only:** participants with acquired resistance to EGFR TKI treatment defined as documented clinical benefit (CR [any duration], PR [any duration], or SD for at least 6 months) on prior first or second generation EGFR TKI therapy (e.g. erlotinib, gefitinib or afatinib); and subsequently demonstrated progression according to RECIST 1.1. • **Phase II Group 2 only:** advanced NSCLC participants who have not been previously treated with any therapy known to inhibit EGFR, who received a maximum of two previous treatment lines of systemic antineoplastic therapies in the advance setting, and harbor de novo T790M mutation as per central assessment. • **Phase II Group 3 only:** participants must be naïve for any systemic antineoplastic therapy in the advanced setting (NSCLC stage IIIB or IV). • **Phase II Group 4 only:** participants who are treatment-naïve or have failed (defined as intolerance to treatment or documented disease progression) a maximum of two previous treatment lines of systemic antineoplastic therapies in the advanced setting. • **Phase II Group 5 only:** • Histologically or cytologically confirmed diagnosis of NSCLC (excluding squamous cell carcinoma) with all the following: • EGFR mutations known to be associated with EGFR TKI sensitivity. This must be assessed as part of the participant standard of care by a validated test for EGFR mutations, as per local regulations. Exon 19 del, L858R, either alone or in combination with other EGFR sensitivity mutation assessed by a Clinical Laboratory Improvement Amendments (CLIA) certified USA laboratory or an accredited local laboratory outside the USA must be documented in the participant source documents before the participant can be consented for pre-screening for MET amplification status. • EGFR T790M negative status for participants who have progressed on first or second generation EGFR TKI, or third generation EGFR TKI other than osimertinib, as per tissue-based result from a CLIA-certified USA laboratory or an accredited local laboratory outside of the USA, by a validated test according to local regulations. Results must be documented in the participant source documents before the participant can be consented for pre-screening for MET amplification. If a local T790M result is not available, T790M status in tissue per central Novartis-desginated laboratory result is required. • MET gene amplification defined as: Gene copy number (GCN) ≥ 5 per tissue-based result from a CLIA-certified USA laboratory or an accredited local laboratory outside of the USA by a test that is validated according to local regulations with results documented in the participant source documents. An adequate amount of tumor tissue (archived or if not available, newly obtained biopsy sample) must be available

	at the time of enrollment for central assessment of MET gene amplification status. If a local result is not available, a tumor tissue sample must be submitted and determined as MET amplified (GCN ≥ 5) per central Novartis-designated laboratory. • Histological transformation from NSCLC into small cell lung cancer (SCLC) following previous EGFR TKI treatment are excluded. • Participants must have progressed on one prior line of therapy either to first/second generation EGFR TKIs, osimertinib or other third generation EGFR TKIs for advanced/metastatic disease (stage IIIB/IIIC [not amenable to curative surgery, chemoradiation or radiation or stage IV NSCLC). Acquired resistance to EGFR TKI treatment is defined as documented clinical benefit (CR [any duration], PR [any duration], or SD for at least 6 months) on prior first/ second EGFR TKIs (e.g., erlotinib, gefitinib, afatinib, dacomitinib), osimertinib or other third generation EGFR TKI such as almonertinib and furmonertinib and subsequently demonstrated radiological disease progression. 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 systemic chemotherapies will count as one prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant or adjuvant systemic therapy. Adjuvant osimertinib therapy will count as prior line of EGFR TKI treatment if relapse occurs during the adjuvant osimertinib therapy. • Participants must have a life expectancy of at least 3 months. • Willing and able to comply with scheduled visits, treatment plan and laboratory tests. Please refer to Section 5.2 for complete list of inclusion criteria.

Key Exclusion criteria	• **Phase Ib:**
	  • More than one previous treatment line with erlotinib, gefitinib or afatinib.
	  • Previous treatment with any investigational agent known to inhibit EGFR (mutant or wild-type).
	  • Participants who have received more than three prior lines of antineoplastic therapy (including EGFR TKI) in the advanced setting.
	• **Phase II:**
	  Group 1:
	  • More than three prior lines of systemic antineoplastic therapies (including EGFR TKI) in the advanced setting.
	  • More than one previous treatment line with first or second generation EGFR TKI (e.g. erlotinib, gefitinib, afatinib) in the advanced setting.
	  • Previous treatment with an investigational or marketed third generation EGFR TKI (e.g. osimertinib, CO-1686, nazartinib).
	  • Previous treatment with other investigational or marketed agent known to inhibit EGFR (e.g. EGF monoclonal antibody therapy, dual TKI inhibitor).
	  Group 2:
	  • More than two previous treatment lines of systemic antineoplastic therapies in the advance setting.
	  • Previous treatment with an investigational or marketed agent that inhibits EGFR. EGFR inhibitors include (but not limited to) all generations of EGFR TKI (e.g. erlotinib, gefitinib, afatinib, osimertinib, CO-1686, nazartinib) or other anti-EGFR or EGF monoclonal antibody therapy or dual TKI inhibitors.
	  Group 3:
	  • De novo EGFR T790M mutation identified by central assessment
	  • Previous treatment with any systemic antineoplastic therapy in the advanced setting (NSCLC stage IIIB or IV). Participants who received only one cycle of systemic antineoplastic therapy in the advanced setting are allowed.
	  Group 4:
	  • More than two previous treatment lines of systemic antineoplastic therapies in the advanced setting.

	• Previous treatment with an investigational or marketed third generation EGFR TKI (e.g. osimertinib, CO-1686, nazartinib). • Previous treatment with an investigational or marketed agent that inhibits EGFR (e.g.: EGF monoclonal antibody therapy or dual TKI inhibitors). • Previous treatment with a MET inhibitor or HGF-targeting therapy • Participants with symptomatic brain metastases. However, participants with asymptomatic/controlled brain metastases may participate in the trial. If treatment is required these participants must have completed any planned radiation therapy and/or surgery > 2 weeks prior to the first dose of study treatment and remain asymptomatic. Participants must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on central nervous system imaging. Participants taking steroids must have been on a stable dose for two weeks prior to the first dose of study treatment. **For Phase II Group 5:** 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. • Presence or history of another malignancy Exception: Participants who have been disease-free for 3 years, or participants with a history of adequately treated in-situ carcinoma of the uterine cervix, completely resected basal or squamous cell carcinoma, non-melanomatous cancer of skin, history of stage IA melanoma that has been cured, are eligible. **For Phase II Group 5:** 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. • Undergone a bone marrow or solid organ transplant. • Known history of human immunodeficiency virus (HIV) seropositivity (HIV testing is not mandatory). For Group 5: Participants with known history of testing positive for human immunodeficiency virus (HIV) infection, and with a history of Acquired ImmunoDeficiency Syndrome (AIDS) defining 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. HIV Participants coinfected with hepatitis virus 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. • Participants receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry except for control of brain metastases, topical applications, inhaled sprays, eye drops or local injections. • Participants with clinically significant, uncontrolled cardiovascular disease, such as: • Unstable angina within 6 months prior to screening. • Myocardial infarction within 6 months prior to screening. • Participants with a history of documented congestive heart failure (New York Heart Association functional classification III-IV). • Participants with uncontrolled hypertension defined as a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.

	• Ventricular arrhythmias. • Supraventricular and nodal arrhythmias not controlled with medication. • Other cardiac arrhythmia not controlled with medication. • Participants with corrected QT (QTc) ≥470 ms using Fridericia correction (QTcF) on the screening electrocardiogram (ECG) (using the average QTcF of the triplicate ECGs). • 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). • Participants have received anti-cancer therapies within the following time frames prior to the first dose of study treatment: • Conventional cytotoxic chemotherapy: ≤ 4 weeks (≤ 6 weeks for nitrosoureas and mitomycin-C). • Biologic therapy (e.g., antibodies): ≤ 4 weeks. • Non-cytotoxic small molecule therapeutics: ≤ 5 half-lives (if half-life known) or ≤ 2 weeks • Other investigational agents: ≤ 4 weeks. • **For Phase II Group 5:** Previous anti-cancer and investigational agents within 4 weeks or ≤ 5 x half-life of the agent (whichever is shorter) before first dose of capmatinib. If previous treatment is a monoclonal antibody, then the treatment must be discontinued at least 4 weeks before first dose of capmatinib. If previous treatment is an oral targeted agent, then the treatment must be discontinued at least 5 x half-life of the agent. • **For Phase II Group 5:** Treatment with a prior first or second generation EGFR TKIs (e.g., erlotinib, gefitinib, afatinib, dacomitinib), osimertinib or another third generation EGFR TKIs within 14 days or approximately 5x half-life, whichever is shorter, of the first dose of study treatment (if sufficient washout time has not occurred due to schedule or PK properties, an alternative appropriate washout time based on known duration and time to reversibility of drug related adverse events could be agreed upon by Novartis and the Investigator). • Radiation therapy (palliative setting is allowed.): ≤ 4 weeks, for asymptomatic brain metastases ≤ 2 weeks. • Major surgery: ≤ 2 weeks **For Phase II Group 5:** Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting capmatinib or who have not recovered from side effects of such procedure. 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. • Participants that have not recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE version 5.0). (Participants with any grade of alopecia are allowed to enter the study). • **Participants in Phase Ib and Phase II Groups 1 to 4** have out of range laboratory values defined as: • Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L (1.5 x 10^3/μL) • Hemoglobin (Hgb) < 9 g/dL (90 g/L) • Platelets (PLT) < 75 x 10^9/L (75 x 10^3/μL) • Total bilirubin > 1.5 x upper limit of normal (ULN) • AST and/or ALT > 3 x ULN, except for participants with liver metastasis who may not be included if AST and/or ALT > 5 x ULN • Alkaline phosphatase (ALP) > 5 x ULN • Calculated creatinine clearance < 45 mL/min using Cockroft-Gault formula • Asymptomatic serum amylase or lipase > Grade 2

	• Serum amylase or serum lipase CTCAE grade ≥ 1 with signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g. elevated P-amylase, abnormal imaging findings of pancreas, etc.) **Participants in Phase II Group 5** have out of range laboratory values defined as: • Absolute Neutrophil Count (ANC) <1.5 x 10^9/L (1.5 x 10^3/µL) without growth factor support • Hemoglobin (Hgb) <9 g/dL (90 g/L) • Platelets (PLT) <100 x 10^9/L (100 x 10^3/µL) • Total bilirubin >1.5 x upper limit of normal (ULN) • AST and/or ALT > 2.5 x ULN except for participants with liver metastasis, who may not be included if AST and/or ALT > 5 x ULN • Alkaline phosphatase (ALP) >5 xULN • Calculated creatinine clearance (using Cockcroft-Gault formula) < 50 mL/min • Asymptomatic serum amylase increase grade 1 and 2 are allowed if at the beginning of the study is 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 • Participants who have impairment of GI function or GI disease that may significantly alter the absorption of study treatment (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome) • **For Phase II Group 5:** Carcinomatous meningitis • **For Phase II Group 5:** Known EGFR T790M positive, Known C797S positive, known druggable molecular alterations (such as ROS1, BRAF, KRAS etc.) who might be candidates for alternative targeted therapies as applicable per local regulations and treatment guidelines • Participants who received live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, Bacille Calmette-Guerin (BCG), yellow fever, varicella, TY21a typhoid vaccines and COVID 19 vaccines) within 30 days prior to the first dose of study treatment Please refer to Section 5.3 for complete list of exclusion criteria
Investigational and reference therapy	nazartinib (EGF816) and capmatinib (INC280)
Efficacy assessments	Tumor assessment per RECIST 1.1 based on investigator's assessment
Safety assessments	Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs.
Other assessments	Plasma concentration vs. time profiles, plasma PK parameters, [redacted].

Data analysis	For the primary objective of Phase Ib, estimation of the maximum tolerated dose (MTD) of the combination treatment will be based upon the estimation of the probability of dose limiting toxicity in cycle 1, using an adaptive Bayesian logistic regression model guided by the escalation with overdose control principle. For the primary objectives of Phase II, the overall response rate (ORR) will be estimated using Bayesian analysis with a minimally informative prior (Groups 1 to 3). For Group 4 the frequency of adverse events will be assessed. For Group 5, the ORR for capmatinib monotherapy will be estimated. The study data will be analyzed and reported based on all participants' data of Phase Ib and Phase II Groups 1 to 4 up to the time when all participants have completed at least six cycles of treatment or discontinued the study treatment earlier. Phase II Group 5 data will be analyzed and reported when all stage 1 and stage 2 participants in this group have completed at least six cycles of treatment or discontinued the study treatment earlier. An interim analysis for ORR is planned in Group 3 when approximately 20 (50%) of the participants have been enrolled and followed up for at least 4 cycles of treatment or discontinued study treatment. The primary intent of this interim analysis is to be able to stop the enrollment of treatment-naïve NSCLC participants in first line NSCLC (Ggroup 3) early if there is evidence of lack of efficacy (futility). No interim analysis is planned for Groups 1, 2 and 4. However, individual participant data will be reviewed on an ongoing basis by the study team across the duration of the trial (Section 8.5). An interim analysis (IA) of the ORR is planned in Group 5 after 10 participants have been enrolled in the stage 1 and followed up for at least 2 tumor assessments while on monotherapy treatment, had radiological disease progression based on investigator's assessment per RECIST 1.1, or discontinued study treatment prior to that time. The intent of this interim analysis is to be able to stop the enrollment if there is evidence of lack of efficacy (futility) of the capmatinib monotherapy. Recruitment will be on temporary halt while conducting the IA. Individual participant data will be reviewed on an ongoing basis by the study team with regard to safety and efficacy.
Key words	NSCLC, nazartinib (EGF816), capmatinib (INC280), TKI, T790M, MET

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

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 were expected in the United States (US) (Siegel et al 2019) and 280,000 in the European Union (Malvezzi et al 2019).

In Western countries, 10-15% non-small cell lung cancer (NSCLC) participants express epidermal growth factor receptor (EGFR) mutations in their tumors (accounting for 20000 to 30000 new participants per year in the USA), and Asian countries have reported rates as high as 30-40%. The predominant oncogenic EGFR mutations (L858R and exon 19 deletion (ex19del)) account for about 90% of EGFR mutant NSCLC. This results in the activation of multiple pathways that promote survival, proliferation, angiogenesis and metastasis (Mendelsohn 2000; Hirsch 2003; Lynch 2004; Paez 2004; Pao 2004). De novo $EGFR^{T790M}$ mutations are rare (<1% of all lung cancers) when identified by standard sensitivity methods and occur concurrently with EGFR mutations L858R or ex19del (Yu et al 2014).

EGFR is an established critical therapeutic target for lung cancer. Numerous trials with first generation EGFR inhibitors (e.g., erlotinib and gefitinib) and more recently with the second generation (e.g., afatinib) have been conducted in the EGFR mutant NSCLC population. These trials have consistently demonstrated superior efficacy of EGFR tyrosine kinase inhibitors (TKIs) over chemotherapy (Table 1-1). EGFR TKIs' response rates in EGFR mutant NSCLC participants range from approximately 60 to 80% versus 20 to 30% for the chemotherapy control arms. Similarly, median progression free survival (PFS) is prolonged via EGFR TKI first line treatment on average by 50%; ranging from 8 to 11 months, as compared to 4 to 6 months for chemotherapy control arms.

Table 1-1 Superiority of EGFR TKIs over chemotherapy in EGFRmut NSCLC

Trial	Compound	RR (%)		Median PFS (mo)		Median OS (mo)	
		TKI	Chemo	TKI	Chemo	TKI	Chemo
IPASS (mut+) (Mok et al 2009)	Gefitinib	71.2	47.3	9.5	6.3	21.6	21.9
First-SIGNAL (mut+) (Han et al 2012)	Gefitinib	84.6	37.5	8.4	6.7	30.6	26.5
WJTOG (Mitsudomi et al 2010)	Gefitinib	62.1	32.2	9.2	6.3	30.9	NR
NEJ002 (Inoue et al 2009)	Gefitinib	73.7	30.7	10.8	5.4	27.7	26.6
OPTIMAL (Zhou et al 2011)	Erlotinib	83	36	13.7	4.6	22.6	28.8
EURTAC (Rosell et al 2012)	Erlotinib	58	15	9.7	5.2	19.3	19.5
Afatinib (LUX-Lung 3) (Keating 2014)	Afatinib	56	23	11.1	6.9	28.1	28.2

Trial	Compound	RR (%)		Median PFS (mo)		Median OS (mo)	
		TKI	Chemo	TKI	Chemo	TKI	Chemo
Afatinib (LUX-Lung 6) (Keating 2014)	Afatinib	66.9	23	11	5.6	22.1	22.2

Although remarkable response rates are seen in participants with EGFR mutations that are treated with EGFR TKIs (~ 80%), the responses are of limited duration because eventually participants develop "acquired resistance".

Several resistance mechanisms have been identified, the most common being a secondary mutation at the threonine gatekeeper residue at position 790, T790M, which develops in up to 50% of NSCLC participants harboring a primary EGFR mutation treated with first or second generation EGFR TKIs. Although the results from the [AURA3] and the [FLAURA] trials led to the approval of osimertinib (a third generation TKI with activity in NSCLCs harbouring the T790M mutation as first- and second-line treatment), it should be noted that 20% of these participants did not respond to osimertinib. C797S mutation was observed in one third of this resistant population, the osimertinib resistance could be linked to the novel C797S mutation, whereas in many other cases MET amplifications as a resistance bypass mechanism causing EGFRmut-TKI resistance have been identified suggesting that a combination of a MET and a EGFRmut inhibitor may be of benefit to overcome the observed resistance in these NSCLC participants (Papadimitrakopoulou et al 2018, Ramalingam et al 2018). The basic mechanism by which MET amplification causes EGFR-TKI resistance is associated with the activation of EGFR-independent phosphorylation of ErbB3 and downstream activation of the PI3K/AKT pathway, providing a bypass signaling pathway even in the presence of an EGFR-TKI (Engelman et al 2007) suggesting that co-targeting both, EGFR and MET is required to overcome resistance to EGFR-TKIs due to MET amplification. The MET amplification in NSCLCs was found to be 2–5%. However, the incidence of MET amplification was higher in NSCLC participants treated with erlotinib or gefitinib, ranging from 5% to 22% (Liang and Wang 2020). Several lines of evidence, however, suggest that MET gene amplification is another important mechanism for TKI resistance in NSCLCs and is detectable in approximately 5–22% of NSCLC participants with acquired resistance to first-generation EGFR-TKIs (Wang et al 2018).

The following results were reported from a phase Ib/II study with capmatinib and gefitinib in NSCLC participants with acquired resistance to gefitinib, erlotinib, or afatinib and MET amplifications (gene copy number ≥ 6) (Wu et al 2018). Overall, 61 participants were treated in phase Ib and 100 participants were treated in Phase II. In the phase Ib part ORR was 23% across all doses and was regardless of the MET status. Increased activity, however, was observed in participants with a high MET copy number, with a Phase II ORR of 47%. The most common drug-related adverse events were nausea (28%), peripheral edema (22%), decreased appetite (21%), and rash (20%). In contrast to a number of other combination studies, the combination of capmatinib and gefitinib was found to be tolerable. From this study the authors concluded that capmatinib in combination with an EGFRmut TKI can restore sensitivity in TKI-resistant NSCLC participants harbouring EGFR mutations. The contribution of a capmatinib alone, however, was not evaluated.

Collectively, MET amplification is observed as one of the key resistant mechanism of EGFR TKIs.

Combination treatment of MET inhibitor and EGFR TKI showed a clinical meaningful response rate in high MET copy number participants who progress on EGFR TKI treatment. However, there is very limited data regarding efficay of MET inhibitor monotherapy in the EGFR TKI resistant population to demonstrate the contribution of component in the combination therapy.

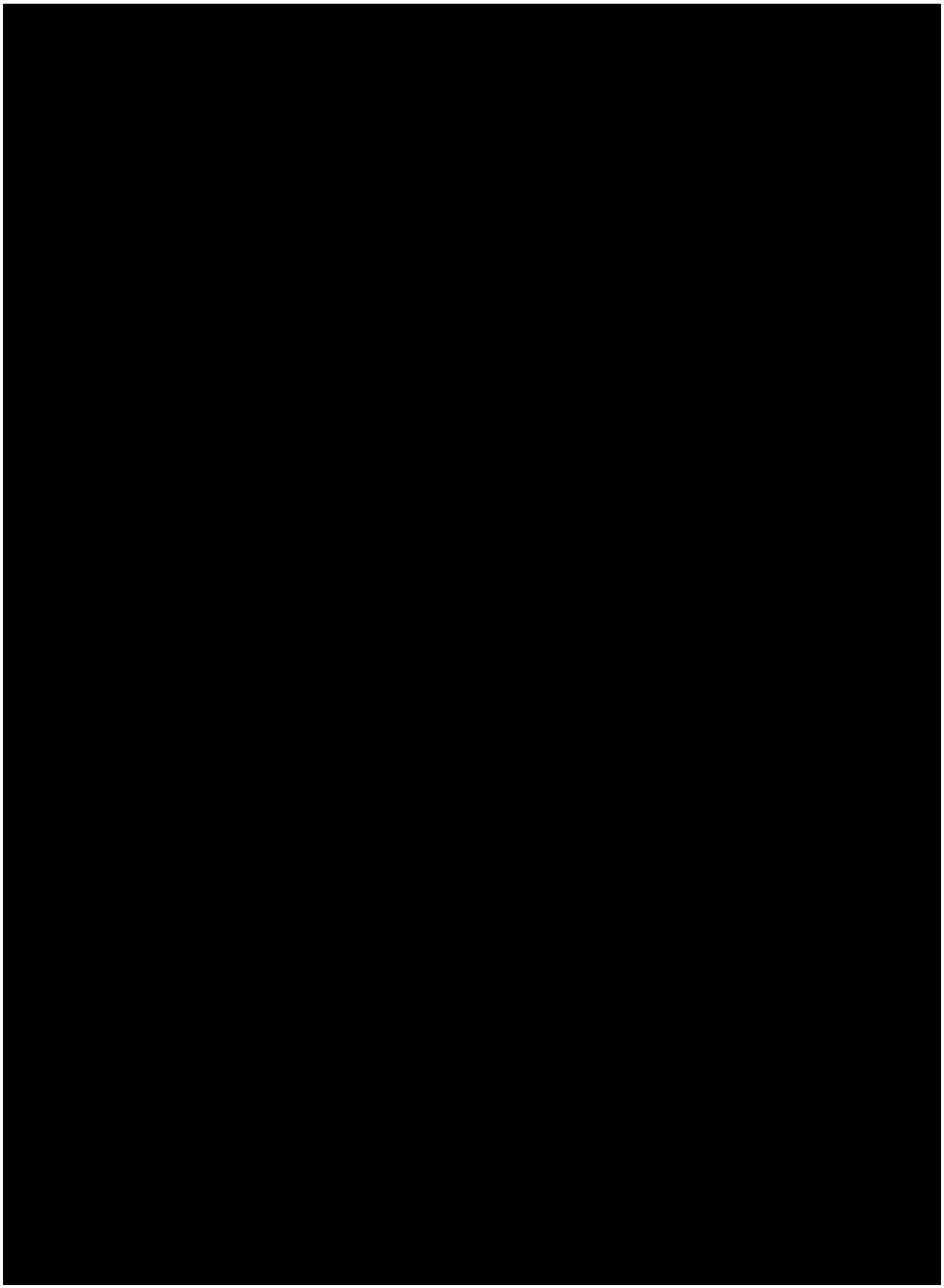
1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of capmatinib (INC280)

Capmatinib (INC280) is a small molecule, 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). Capmatinib is currently approved by the FDA for the treatment of adult participants with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping mutation. Approval has been reported also in Japan, Brazil, Switzerland, Taiwan, India and Hong Kong.

Based on the efficacy and safety data from Phase II GEOMETRY 1 study [CINC280A2201]: in previously treated participants with locally advanced or metastatic NSCLC harboring MET 14 exon skipping mutation, Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 confirmed major responses (including a complete response [CR]) evaluated by Blinded Independent Review Committee (BIRC) were observed in 28 out of 69 (ORR 41%, [95% CI, 29-53) evaluable participants (defined as those with at least one post-baseline tumor assessment or have discontinued treatment at the time of the data cut-off) and median DOR was 9.7 months [95% CI 6-13.0]. Median progression-free survival (mPFS) was 5.4 months [95% CI 4.2 – 7.0]. Moreover, intracranial responses were observed in 7 out of 13 evaluable participants with brain metastases at baseline. Four participants had complete resolution of lesion (Wolf et al 2020).

Please refer to the current [capmatinib Investigator's Brochure] for more detailed information.



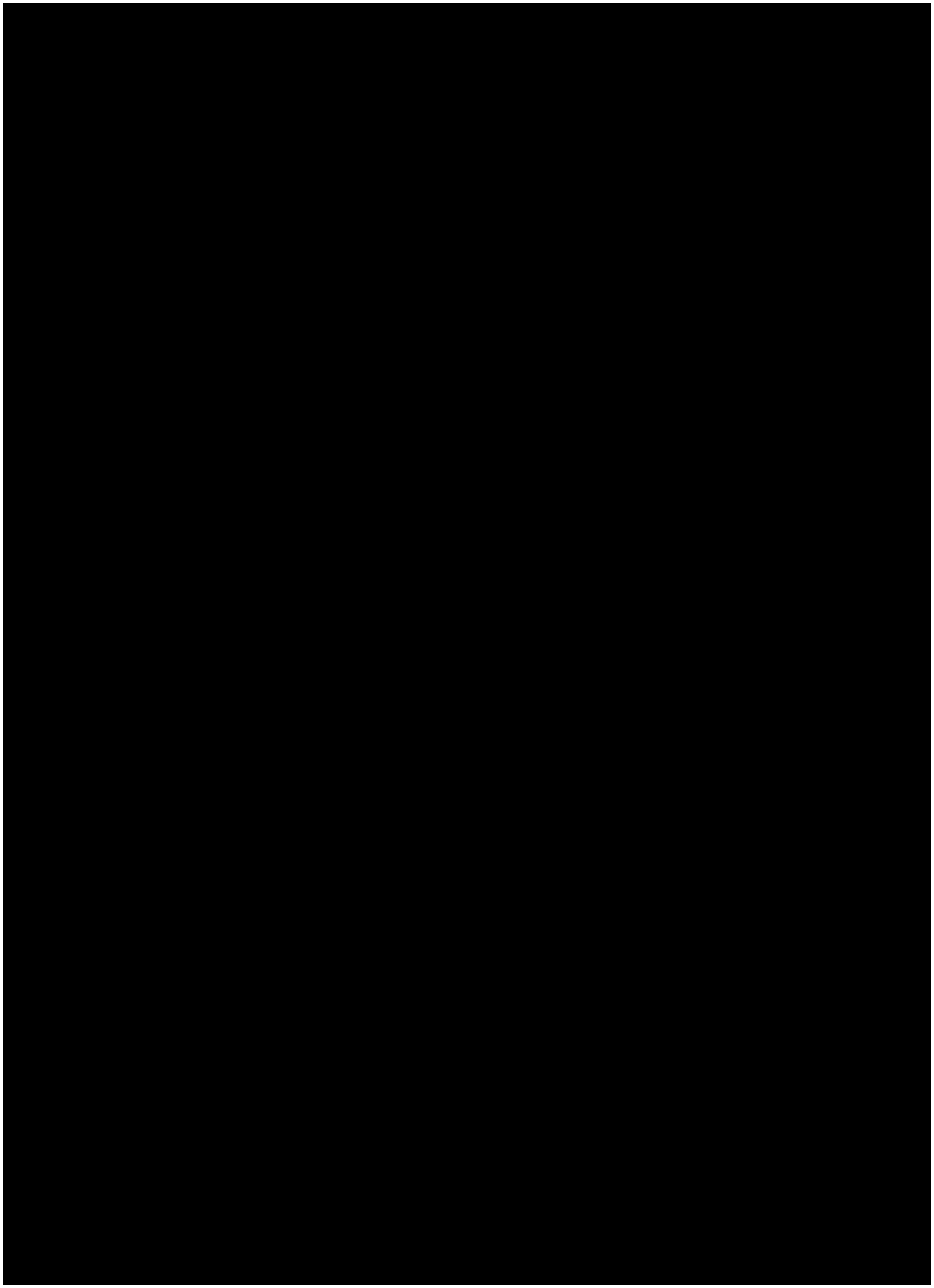
[redacted]

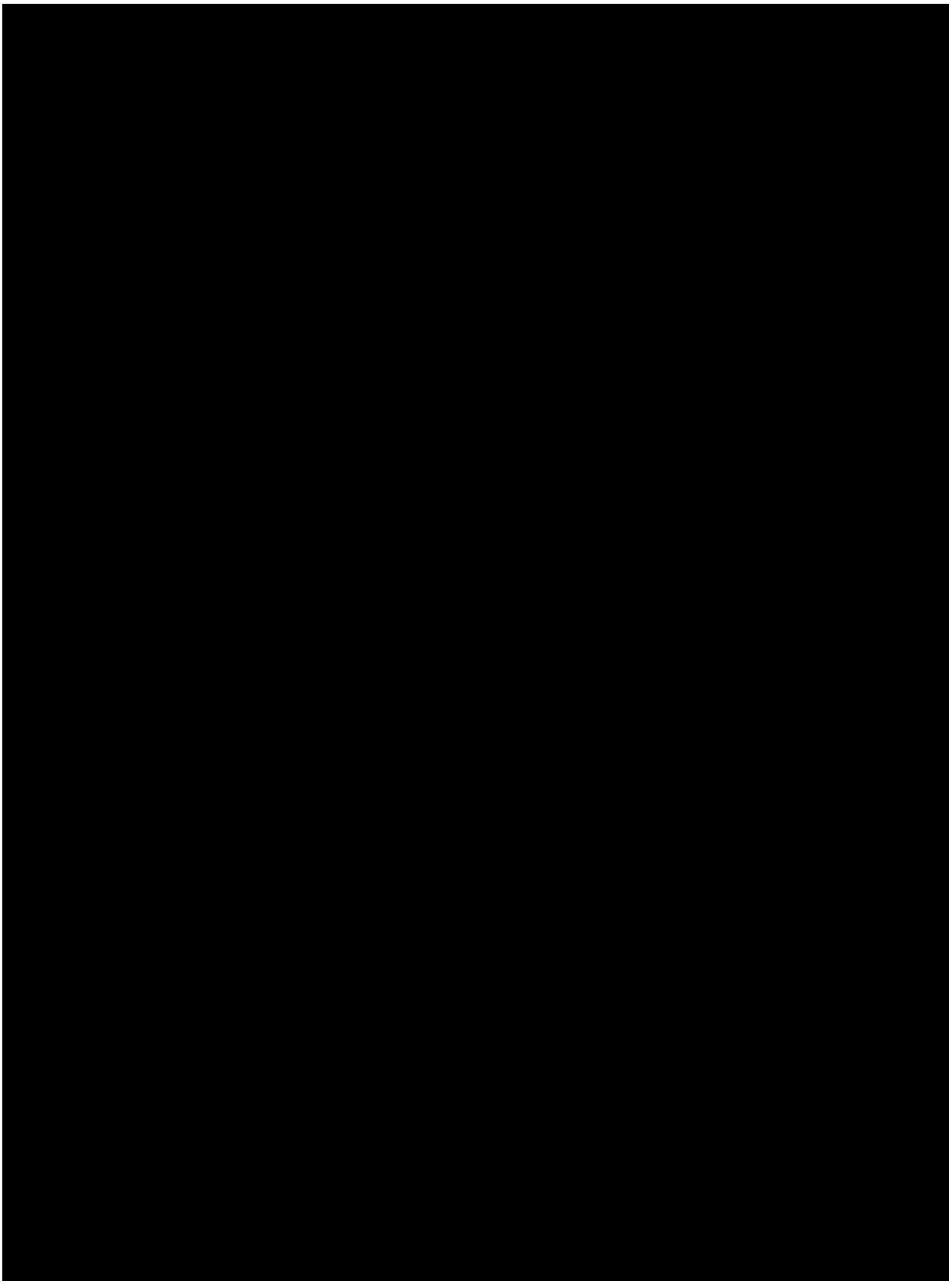
1.2.2 Overview of nazartinib (EGF816)

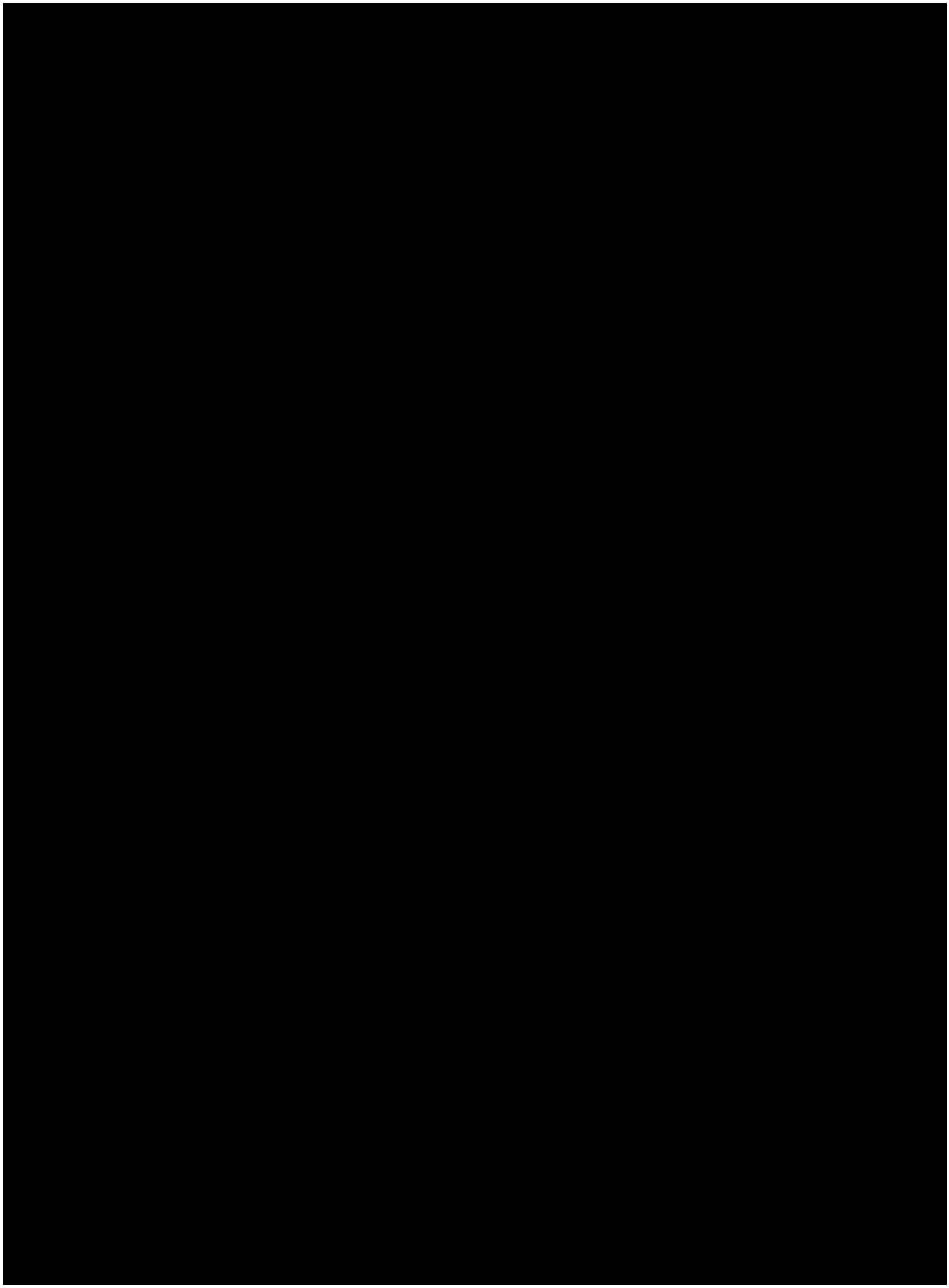
Nazartinib is a targeted covalent irreversible EGFR inhibitor that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M), while sparing WT EGFR.

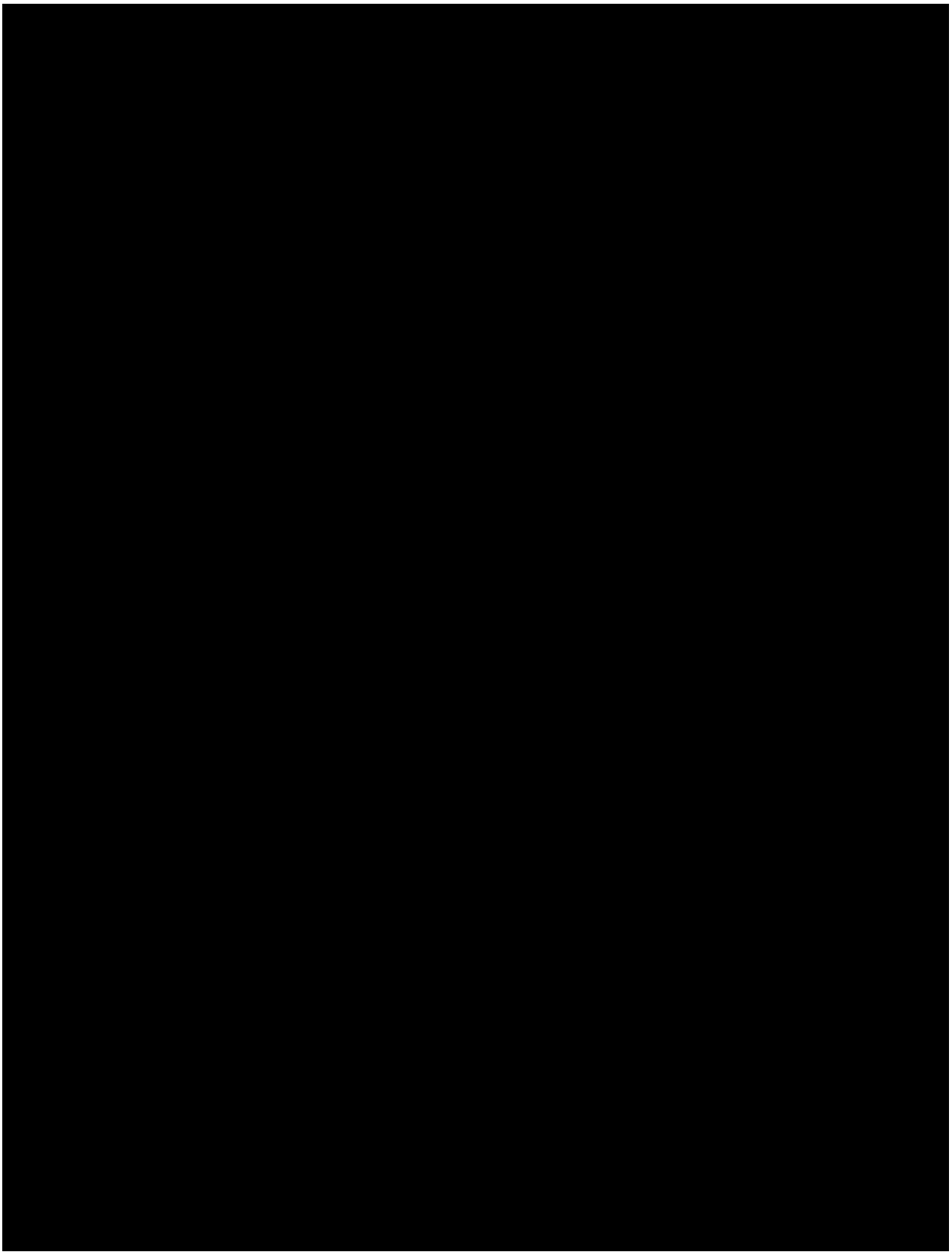
Nazartinib has shown significant efficacy in EGFR mutant (L858R, ex19del and T790M) cancer models (in vitro and in vivo) with no indication of WT EGFR inhibition at efficacious concentrations.

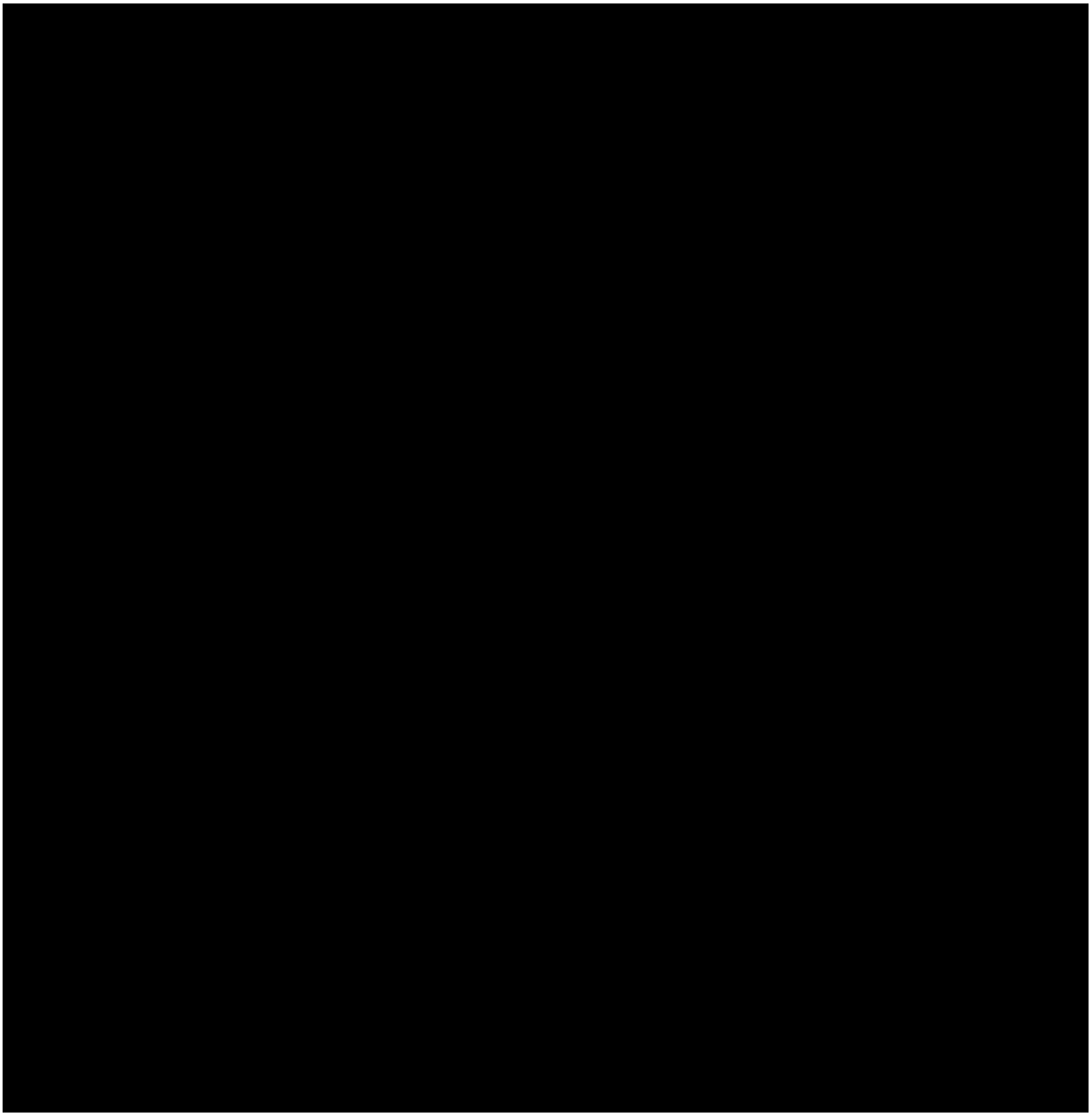
[redacted]











2 Rationale

2.1 Study rationale and purpose

Currently approved first and second generation EGFR TKIs are effective in activated EGFR mutant NSCLC (Section 1.1), however nearly all participants develop resistance.

Documented mechanisms of acquired resistance to nazartinib include EGFR C797S mutations, deletion in mTOR, B-RAF fusions, MET amplification, and concurrent p53 and RB1 truncating mutations associated with small cell transformation (Tan et al 2017). Currently it is unclear if the prevalence of resistance alterations with this compound differs significantly to osimertinib.

Interestingly, dual inhibition of EGFR and MET with nazartinib and capmatinib demonstrated significant tumour regression using in vitro models (Jia et al 2016).

Nazartinib, novel third generation EGFRmut TKI, was chosen as the drug has shown a greater activity against EGFR exon 20 insertions when compared with osimertinib (Murtuza et al 2019). EGFR exon 20 insertion mutations are typically located just after the C-helix of the tyrosine kinase domain of EGFR, and their incidence varies between 1% to 9% of all EGFR mutations (Byeon et al 2019). Moreover, participants with EGFR exon 20 insertions who received a EGFRmut TKI were found to have low ORRs and a short mPFS (2.4 months) (Naidoo et al 2015). Although being rare these mutations should not be overlooked due to the poor outcome following TKI treatment.

Based on preclinical data for nazartinib and the known clinical responses to other EGFR inhibitors in NSCLC participants harboring EGFR mutations, it is expected that significant activity will be observed in NSCLC participants harboring the activating EGFR mutations (L858R and ex19del) and/or the acquired/resistant "gatekeeper" mutation T790M; and while sparing WT EGFR, nazartinib will be better tolerated than current available treatment options. Nazartinib is a third generation irreversible EGFR TKI that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M+), while sparing WT EGFR. Taken together, these two properties of nazartinib should translate into longer sustained responses and improvement in safety profile or tolerability compared to currently available therapy.

On the other hand, another mechanism of acquired resistance to EGFR tyrosine kinase inhibitors is MET proto-oncogene amplification in NSCLC (Engelman 2007; Salgia 2009; Cappuzzo 2009a, Cappuzzo 2009b). [redacted] It has been shown that MET overexpression is present as primary mechanism of resistance in EGFR mutated EGFR TKI naïve NSCLC participant which supports administration of MET inhibitor in combination with EGFR TKI in first line setting. Despite high response rates to EGFR TKIs, most participants with EGFR-mutant NSCLC ultimately relapse (Kobayashi et al 2005). Dysregulation of the MET pathway is implicated as a therapeutically tractable resistance mechanism. MET is amplified in 21% of NSCLCs with EGFR TKI resistance, and dysregulated in 57% of EGFR-mutant NSCLC participants (Bean 2007; Huang 2014).

[redacted]

Beside this, there is evidence showing that administration of MET inhibitor in combination with EGFR TKI would prevent resistance (Section 1.1).

In order to explore the hypothesis that targeting the activating resistance mutants together with the two main EGFR resistance mechanisms, T790M and MET, may prevent the acquisition of resistance to EGFR TKIs or overcome the acquired resistance to EGFR TKIs, this study will

combine the third generation EGFR TKI, nazartinib, and the highly selective and potent MET inhibitor, capmatinib, in NSCLC participants with documented EGFR mutation (L8585R, ex19del) in first line setting or who have developed resistance to EGFR TKI treatment.

Based on the preliminary clinical efficacy and safety data observed in NSCLC participants who received capmatinib in combination with nazartinib (a third generation EGFR TKI) therapy in this study, the Sponsor plans to establish the role of capmatinib in combination with the third generation EGF TKI in a population of participants with EGFRm, T790M negative, MET amplified, progressed on prior line of EGFR TKI treatment NSCLC. However, it is necessary to also consider the contribution of components; [redacted] Furthermore, the contribution of capmatinib as monotherapy needs to be established in this EGFR mutant setting which then will pave the the way for the optimal use of the combination in future trials.

There is limited data on the safety and efficacy of capmatinib monotherapy in NSCLC EGFR resistant MET amplified (Gautschi et al 2020) supporting further the proposed investigation. From the data provided by Wolf et al. (2020) which indicated that the median time to response for capmatinib was 6 weeks, data from this arm can be adequately regarded as a measure for the contribution of capmatinib monotherapy in this setting and will provide a significant step to further evaluate this new treatment strategy.

2.2 Rationale for the study design

Phase Ib part

The design of the Phase Ib, open label, dose finding part of this study was chosen to establish the MTD/RP2D of nazartinib in combination with capmatinib in participants with NSCLC who have a locally documented EGFR mutation (L858R, ex19del) and progressed on EGFR TKI treatment (e.g., erlotinib, gefitinib or afatinib). The dose escalation will be guided by a Bayesian Logistic Regression Model (BLRM).

This open-label dose escalation study design using a BLRM is a well-established method to estimate the MTD/RP2D in cancer participants. The adaptive BLRM will be guided by the escalation with overdose control (EWOC) principle to control the risk of dose limiting toxicity (DLT) in future participants on study. The use of Bayesian response adaptive models for small datasets has been accepted by EMEA ("Guideline on clinical trials in small populations" February 1, 2007) and endorsed by numerous publications (Babb 1998, Neuenschwander 2008, Neuenschwander 2010, Neuenschwander 2014), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

The decisions on new dose combinations are made by the Investigators and Novartis study personnel and will be guided by the BLRM, and based upon participant tolerability and safety, PK and efficacy information available at the time of the decision (Section 6.2.3).

Phase II part

Once the MTD or RP2D has been defined, the Phase II part will open at the MTD or RP2D.

The design of the Phase II part is to characterize the anti-tumor activity, safety, tolerability and PK of nazartinib and capmatinib when administered in combination at the selected dose in NSCLC participants with documented activating EGFR mutation (L858R, ex19del) or de novo T790M mutation. The primary endpoint of antitumor activity is the overall response rate (ORR) per RECIST 1.1 as determined by the Investigators' assessment.

The Phase II part will consist of 5 groups (Figure 4-1), each having distinctive enrollment criteria and a different rationale for exploration.

For the purpose of this study, common EGFR activating/sensitizing mutations are L858R point mutation and exon 19 deletions which account for approximately 90% of the cases. Other rare EGFR mutations such as L861Q, G719X, and S768I are also considered activating/sensitizing mutations for enrollment onto the Phase II part.

The acquired resistance mutants are defined as follows:

- "T790M positive" or "T790M+" when the T790M mutation is present;
- "MET dysregulation positive" or "MET dysregulation+" when tumor sample analysis shows either:
  - IHC 3+ (defined as ≥50% of cells staining with high intensity) and/or
  - MET gene copy number ≥ 4

In Group 5 "MET amplification" is defined as MET gene copy number (GCN) ≥ 5

In addition, a treatment line is defined as a combination of medications, or single-agent medication, used to treat the disease indication. If the medication in a single-agent treatment line or any of the medication(s) in a combination therapy were interrupted due to reasons other than disease progression (for example: toxicity, physician's decision, etc.), and this was followed by re-challenge with the same medication or different 'substitute' medication(s), without evidence of progression, then all of these medications should be considered as a single treatment line.

Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant)

Group 1 will enroll at least 40 NSCLC participants with locally documented activating EGFR mutation (L858R, ex19del) who received one to three lines of systemic antineoplastic therapy prior to study entry including one line maximum of first or second generation EGFR TKI (e.g., erlotinib, gefitinib, afatinib) and who progressed on this EGFR TKI treatment line.

The participants in Group 1 will be assigned according to their acquired resistance mechanism in 4 sub-groups:

- 1a. $EGFR^{L858R/ex19del}$ NSCLC with acquired mutation T790M
  (T790M+, MET dysregulation-)
- 1b. $EGFR^{L858R/ex19del}$ NSCLC with demonstrated MET dysregulation
  (T790M-, MET dysregulation+)
- 1c. $EGFR^{L858R/ex19del}$ NSCLC with both acquired T790M and MET dysregulation
  (T790M+, MET dysregulation+)

- 1d. $EGFR^{L858R/ex19del}$ NSCLC with MET dysregulation below the levels for sub-group 1b *(T790M-, MET dysregulation-)*

A minimum of 20 participants harboring the EGFR T790M mutation will be enrolled among subgroups 1a and 1c, and a minimum of 20 participants who do not have the T790M mutation will be enrolled among the subgroups 1b and 1d.

In Group 1, the participants will enter the study in the second to forth line setting, i.e., will have received before study entry a maximum of 3 prior lines of systemic antineoplastic therapies (chemotherapy and/or targeted therapies) in the advanced setting including one line maximum of first or second generation EGFR TKI.

Treatment of NSCLC with EGFR activating mutations (e.g., L858R and/or ex19del) with first- or second-generation EGFR TKIs often results in dramatic responses; however, those are of limited duration and eventually participants develop "acquired resistance". The most frequently reported mechanism of acquired resistance is the EGFR T790M mutation (Kobayashi et al 2005; Pao et al 2005), which accounts for up to 60% of cases. Nazartinib is a third generation irreversible EGFR TKI that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M), while sparing WT EGFR. [redacted]

In addition, with treatment of other third generation EGFR TKIs such as osimertinib, promising clinical activity has been observed in participants who progressed on a first or second generation EGFR TKI but who did not acquire the T790M mutation (Jänne et al 2015). Due to similar mechanism of action, nazartinib may have similar clinical activity in this participant population.

On the other hand, MET amplification is another mechanism of resistance for EGFR TKIs. Recent clinical studies suggest that inhibitors of MET may provide a valuable therapeutic option in the treatment of NSCLC with dysregulated MET signaling (Camidge et al 2014). Capmatinib is an orally bioavailable highly potent and selective MET inhibitor capable of blocking MET activation. It is expected that the co-administration of a MET inhibitor with a third generation EGFR TKI overcomes or prevents the acquisition of resistance mechanisms in participants who progressed on a prior line of first or second generation EGFR TKI.

Therefore Group 1 will focus on further characterizing the efficacy, safety and tolerability of capmatinib in combination with nazartinib in locally advanced or metastatic NSCLC who previously progressed on a prior line of first or second generation EGFR TKI.

Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve)

Group 2 will enroll NSCLC participants harboring T790M mutation in de novo setting (i.e., prior to treatment with any EGFR inhibitor therapy, including anti-EGFR monoclonal antibodies and dual TKI inhibitor), irrespective of the activating mutation status. This group will focus on exploring the preliminary efficacy and tolerability of nazartinib and capmatinib combination in this rare population of participants who have de novo resistance to current EGFR TKI therapy and for which third generation EGFR TKI, nazartinib, has been designed to inhibit in addition to preventing the acquisition of resistance to EGFR TKIs through MET

dysregulation with capmatinib. The estimated incidence of "de novo" T790M mutation is low (~1%). Thus, the sample size is limited to approximately 5 participants if any are identified before the enrollment in the other groups is completed, in order to allow completion of enrollment within a reasonable timeframe.

In Group 2, the participants will enter the study in the first to third line setting, i.e. will be treatment naïve or have received a maximum of 2 prior lines of systemic antineoplastic therapies (chemotherapy and/or targeted therapies) in the advanced setting before study entry, but no therapy known to inhibit EGFR.

Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic)

Group 3 will enroll a minimum of 40 participants who have locally advanced or metastatic NSCLC with locally documented EGFR activating mutation (L858R, ex19del). The participants will have not received any systemic antineoplastic therapy (chemotherapy and/or targeted therapies) for advanced NSCLC before study entry and will be eligible to receive EGFR TKI treatment. Nazartinib is a third generation irreversible EGFR TKI that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M), while sparing WT EGFR. Inhibitors of EGFR-mutant L858R and ex19del, such as first and second generation EGFR TKIs, have been well validated as therapeutic agents for advanced NSCLC participants who are treatment naïve. Novel EGFR therapies such as third generation EGFR TKIs can also target the primary activating mutations. [redacted] Other third generation EGFR TKIs, such as osimertinib, have shown promising preliminary data in this participant population (Jänne et al 2015). Osimertinib has ongoing Phase III clinical trials in the first line setting. Based on the mechanism of action, nazartinib will likely have similar clinical activity in this participant population. In addition, it is expected that the co-administration of a highly potent MET inhibitor with an EGFR TKI will prevent the development of resistance in the first line setting.

In Group 3, the participants will enter the study in the first line setting, i.e. will not have received any prior line of systemic antineoplastic therapies (chemotherapy and/or targeted therapies). Participants having received a maximum of one cycle of systemic antineoplastic therapy are allowed, but no cycle of targeted therapy is allowed.

Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic

Group 4 will enroll approximately 30 participants under fed conditions (unrestricted meal type). All participants must have locally advanced or metastatic NSCLC with locally documented EGFR activating mutation. The participants can be treatment naïve or have failed a maximum of 2 prior lines of any systemic antineoplastic therapy for advanced NSCLC.

The main purpose of this group is to allow assessment of safety and pharmacokinetics of the combination therapy when received with food.

A Bayesian design is implemented in each Group of the Phase II part from which the posterior distribution of the true overall response rate will be used to estimate the chance of significant

clinical activity. Details of the statistical designs are provided in Section 10.5.2 and sample size requirements are provided in Section 10.10.

Group 5 (EGFRmut, T790M-, MET GCN≥5, 2L, EGFR TKI resistant)

Treatment of NSCLC with EGFR activating mutations (e.g., L858R and/or ex19del) with EGFR TKIs often results in dramatic responses; however, those are of limited duration and eventually participants develop "acquired resistance". The most frequently reported mechanism of acquired resistance is the EGFR T790M mutation for first and second generation EGFR TKIs (Kobayashi et al 2005; Pao et al 2005), which accounts for up to 60% of cases. Nazartinib is a third generation irreversible EGFR TKI that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M), while sparing WT EGFR. Preliminary efficacy results from the Phase I part of [CEGF816X2101] in advanced NSCLC participants with both EGFR activating mutation (L858R and/or ex19del) and an acquired EGFR T790M mutation showed significant antitumor activity of nazartinib that is in line with other third generation EGFR TKIs, and a tolerable safety profile.

MET amplification is another mechanism of resistance for EGFR TKIs. Recent clinical studies suggest that inhibitors of MET may provide a valuable therapeutic option in the treatment of NSCLC with dysregulated MET signaling (Camidge et al 2014). Capmatinib is an orally bioavailable highly potent and selective MET inhibitor capable of blocking MET activation. It is expected that the co-administration of a MET inhibitor with a third generation EGFR TKI overcomes or prevents the acquisition of resistance mechanisms in participants who progressed on EGFR TKI.

Therefore Group 5 will focus on further characterizing the efficacy, safety and tolerability of capmatinib monotherapy in locally advanced or metastatic NSCLC who previously progressed on a prior line of EGFR TKI with acquired MET amplification but T790M negative.

2.3 Rationale for dose and regimen selection

In this study, the selection of the dosing regimen of capmatinib and nazartinib is based on the currently available human safety, efficacy and PK information for capmatinib, and preclinical safety, efficacy, PK and PK/PD information for nazartinib. [redacted]

The starting dose of capmatinib will be 200 mg b.i.d. (tablet formulation) and, as per Health Authority request the starting dose of nazartinib will be 50 mg q.d. on a continuous daily dose. The selection of the starting dose of capmatinib and nazartinib is based on currently available non-clinical and clinical data as well as the drug-drug interaction (DDI) potential assessment for this combination regimen. [redacted]

Refer to the [nazartinib and capmatinib Investigator's Brochures] for further information and section 1.2.1 for capmatinib monotherapy

Consistent with its approved label, capmatinib single agent can be administered with or without food.

The selected starting dose of nazartinib 50 mg q.d. in combination with capmatinib tablet starting dose of 200 mg b.i.d., is supported by the risk assessment (EWOC) within the BLRM derived from current single-agent dose-DLT data and predicted interaction.

2.4 Rationale for choice of combination drugs

This study is designed to explore if the combination of the EGFR inhibitor, nazartinib, and MET inhibitor, capmatinib, will provide clinical benefit to 1) NSCLC participants whose tumors have developed resistance to EGFR TKI treatment through acquiring T790M mutation and/or MET pathway dysregulation and possibly overcome this resistance as well as 2) NSCLC EGFR inhibitor treatment naïve participants who harbor T790M de novo mutation and possibly overcome this resistance and prevent acquiring resistance through MET dysregulation (Section 2.1).

2.5 Rationale for choice of comparator drugs

Not applicable.

2.6 Risks and benefits

The purpose of this study is to investigate capmatinib in combination with nazartinib in adult participants with advanced/metastatic non-small cell lung cancer, harboring EGFR mutations (e.g.: L858R and/or ex19del) and provide a new and valuable therapeutic option for this participant population. Preclinical as well as clinical data suggest that the combination of capmatinib plus nazartinib may overcome the acquisition of resistance to EGFR TKIs or overcome the acquired resistance to EGFR TKIs. [redacted]

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules, are included in Section 5 and Section 6 of this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.3. The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures as well as close safety lab and clinical monitoring.

During the dose escalation part of the study, all available safety and pharmacokinetic data were reviewed by participating investigators and Novartis at dose escalation meetings after the completion of each cohort in the phase Ib. The RP2D dose was determined at the dose level of capmatinib 400 mg b.i.d. + nazartinib 100 mg q.d. Capmatinib 400 mg b.i.d. correspond to the recommended dose utilized for monotherapy clinical studies. Refer to the [nazartinib and capmatinib Investigator's Brochures] for further information.

The treating physician must inform the Novartis medical monitor if, during the treatment period, any signs or symptoms are observed that are not consistent with the toxicities discussed in the [capmatinib Investigator's Brochure] and [nazartinib Investigator's Brochure]. The potential risks associated with the combination therapy will be carefully assessed and monitored following the procedure defined in the protocol.

The preliminary clinical safety data from the combination therapy indicate that the majority of adverse events receiving capmatinib and nazartinib (regardless of dose and formulation) have been mild or moderate. In addition, this study incorporates routine safety monitoring and regularly scheduled assessments to identify and report any adverse event or potential safety issues. However, there may be unforeseen risks with any study treatment which could be serious. Refer to the [capmatinib Investigator's Brochure] and [nazartinib Investigator's Brochure] for further information.

Based on the available data, the overall risk/benefit assessment of nazartinib in combination with capmatinib is supportive of the conduct of this study in NSCLC participants in the context of this study.

2.7 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 are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by local or regional health authorities and ethics committees as appropriate.

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.5.4.
Phase Ib: To estimate the MTD or RP2D of nazartinib in combination with capmatinib	Incidence of DLTs	
Phase II: To estimate the preliminary anti-tumor activity of nazartinib in combination with capmatinib (Groups 1, 2 and 3)	Objective response rate (ORR) per RECIST 1.1 based on investigator's assessment	
To characterize the safety and tolerability of nazartinib in combination with capmatinib when taken with food (Group 4)	Safety: Incidence and severity of AEs and SAEs Tolerability: Dose interruptions, reductions and dose intensity	
To estimate the preliminary anti-tumor activity of capmatinib monotherapy (Group 5)	ORR per RECIST 1.1 based on investigator's assessment for capmatinib monotherapy	Refer to Section 10.6.
Secondary		Refer to Section 10.7.
Phase Ib/II (Groups 1 to 4): To characterize the safety and tolerability of nazartinib in combination with capmatinib	Safety: Incidence and severity of AEs and SAEs, including changes in hematology and chemistry values, vital signs and ECGs Tolerability: Dose interruptions, reductions and dose intensity	
Phase Ib: To evaluate the preliminary anti-tumor activity of nazartinib in combination with capmatinib	ORR, PFS, time to response (TTR), duration of response (DOR) and disease control rate (DCR) based on investigator's assessment and overall survival (OS)	
Phase II (Groups 1 to 4): To evaluate the preliminary anti-tumor activity of nazartinib in combination with capmatinib	PFS, TTR, DOR, DCR and ORR (Group 4 only) based on investigator's assessment and OS	
Phase Ib/II (Groups 1 to 4): To characterize the PK of nazartinib and capmatinib when given in combination under fasted state or with food	Plasma concentration vs time profiles. Plasma PK parameters of nazartinib and capmatinib	
Phase II (Group 5):		
To estimate the preliminary anti-tumor activity of capmatinib monotherapy	DOR, DCR, and PFS based on investigator's assessment for capmatinib monotherapy	
To characterize the safety and tolerability of capmatinib monotherapy as well as capmatinib in combination with nazartinib therapy	Safety: Incidence and severity of AEs and SAEs, including changes in hematology and chemistry values, vital signs and ECGs Tolerability: Dose interruptions, reductions and dose intensity	

Objective	Endpoint	Analysis
[redacted]		
ORR is defined as proportion of participants with best overall response of PR+CR per RECIST 1.1; DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause; DCR is defined as the proportion of participants with best overall response of CR, PR, or SD; PFS is defined as the time from the date of first dose of study treatment to the date of first documented disease progression (per RECIST 1.1) or death due to any cause; TTR is defined as the time between date of start of treatment until first documented response (CR or PR); OS is defined as the time from first dose of study treatment to the date of death due to any cause.		

4 Study design

4.1 Description of study design

This study has been designed as a Phase Ib/II, multi-center, open-label study starting with a Phase Ib dose escalation part followed by a Phase II part. Oral nazartinib (once daily) and capmatinib (twice daily) will be administered on a continuous schedule until participant experiences unacceptable toxicity, progressive disease and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent/opposition to use data/biological samples.

Note: the study treatment may be continued beyond RECIST 1.1 defined progressive disease if, in the judgment of the investigator, there is evidence of clinical benefit and the participant wishes to continue with the study treatment. The judgment of the investigator should be documented in the Case Report Form (CRF) and the continued evidence of clinical benefit should be updated on a regular basis.

In Phase Ib and Phase II Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant), Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic),Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antioneoplastic, with food) and Group 5 (EGFRmut, T790M-, MET GCN≥5, EGFR TKI resistant) participants with NSCLC harboring EGFR activating mutations (L858R and/or ex19del, additionally other rare mutations L861Q, G719X, or S768I will satisfy eligibility criteria) will be enrolled. For Phase II Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve), participants with NSCLC, harboring de novo EGFR T790M mutation, without prior EGFR TKI treatment will be enrolled.

In the Phase Ib part at least 18 participants who have progressed on previous EGFR TKI treatment (e.g., post erlotinib, gefitinib or afatinib) will be enrolled. An adaptive BLRM with EWOC will guide the dose escalation to determine the MTD or RP2D. Before a drug dosage can be declared to be the MTD or RP2D, at least six participants should have been treated at that dosage.

Once the MTD or RP2D has been declared, additional participants with NSCLC will be enrolled in the Phase II part as shown in Figure 4-1 in order to assess the preliminary anti-tumor activity of nazartinib in combination with capmatinib.

In the Phase II Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant), participants with a previously documented EGFRmut$^{L858R/ex19del}$ NSCLC, who develop resistance to EGFR TKI treatment (e.g., post erlotinib, gefitinib or afatinib) will be enrolled and assigned according to their acquired resistance mechanism to one of four sub-groups:

- sub-group 1a: EGFRmut$^{L858R/ex19del}$ NSCLC with acquired mutation T790M *(T790M+, MET dysregulation-)*.
- sub-group 1b: EGFRmut$^{L858R/ex19del}$ NSCLC with demonstrated MET dysregulation *(T790M-, MET dysregulation+)*.

MET dysregulation is defined as either

a. IHC 3+ (defined as ≥50% of cells staining with high intensity) and/or
b. MET gene copy number ≥ 4

- sub-group 1c: EGFRmut$^{L858R/ex19del}$ NSCLC with evidence of both acquired T790M and MET dysregulation *(T790M+, MET dysregulation+)*.
- sub-group 1d: EGFRmut$^{L858R/ex19del}$ NSCLC with MET dysregulation below the levels for sub-group b *(T790M-, MET dysregulation-)*.

Please refer to Section 5.1 and Section 7.1.1 for further details.

At least 40 participants will be enrolled in the Phase II part Group 1 with a minimum of 20 participants harboring the T790M mutation among sub-groups 1a and 1c, and a minimum of 20 participants who do not harbor the T790M mutation among sub-groups 1b and 1d.

As per literature, it is expected that 50% of participants will acquire T790M mutation (Kosaka 2006; Balak 2006; Engelman 2007; Bean 2007), 20 to 40% will develop MET dysregulation (Salgia 2009; Cappuzzo 2009a; Cappuzzo 2009b; Engelman 2007) and 10 to 20% will present other alterations. The participants must have received a maximum of 3 prior lines of systemic antineoplastic therapies (including one line maximum of EGFR TKI) at time of study entry.

The Phase II part Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve) will enroll approximately 5 NSCLC participants who are EGFR inhibitor treatment (including anti-EGFR monoclonal antibodies and dual inhibitor) naïve and harbor T790M de novo mutation. The participants may harbor or may not harbor an EGFR activating mutation (L858R and/or ex19del) in addition to the EGFR T790M mutation of resistance. The incidence of de novo T790M mutation is rare (□1%). The enrollment in Group 2 will stop once the enrollment in the other groups is completed to allow for completion of recruitment within a reasonable timeframe. [redacted] Note: participants may have received a maximum of 2 prior lines of systemic antineoplastic therapies, but no prior lines of EGFR TKI treatment or anti-EGFR monoclonal antibodies.

In the Phase II Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic), a minimum of 40 participants with documented EGFRmut$^{L858R/ex19del}$ NSCLC, who have never received any systemic antineoplastic therapy will be enrolled. Note: participants who have received no more than 1 cycle of systemic antineoplastic therapy in the advanced setting are allowed.

In the Phase II Group 4 (EGFRmut, any T790M, any MET, 1/3L antineoplastic) approximately 30 participants, with documented EGFRmut NSCLC, who have never received any systemic antineoplastic therapy or have failed a maximum of 2 lines of antineoplastic therapies for advanced disease will be enrolled. Group 4 participants will take study drugs with food (unrestricted meal type) whilst participants from all other groups will take the study drugs under fasting conditions. Approximately 10 participants who are treatment-naïve for advanced setting should be enrolled in Group 4, in order to collect some safety information on this participant population.

Treatment-naïve participants should be enrolled in Group 3 as priority before being enrolled into Group 4. De novo T790M participants should be enrolled into Group 4 as priority before being enrolled into Group 2.

In the Phase II Group 5 (EGFRmut, T790M-, MET GCN≥5, 2L, EGFR TKI resistant) approximately 30 NSCLC participants with locally documented activating EGFR mutation (e.g., L858R, ex19del) who must have progressed on one prior line of therapy (either to first/second generation EGFR TKIs, osimertinib or other third generation EGFR TKIs) for advanced/metastatic disease (stage IIIB/IIIC [stage IIIB/IIIC [not amenable to curative surgery, chemoradiation or radiation] or stage IV NSCLC) will be enrolled in a two-stage design. Enrollment of participants who have progressed on prior line with osimertinib will be a minimum of 50% of the planned total number of participants while participants who progressed on other third generation EGFR TKI will represent a maximum of 10% of the planned total number of participants.

In Stage 1, 10 MET amplified (centrally confirmed) participants, among which at least 50% priorly treated with osimertinib will be enrolled. The decision to continue enrollment in Stage 2 will be based on the futility interim analysis evaluating the ORR as per RECIST 1.1 while on capmatinib monotherapy treatment (see Section 4.2). If futility is concluded, the study will not proceed to Stage 2. If the Group 5 is not declared futile, additional 20 participants will be enrolled in Stage 2.

To adjust for potential discordance between local vs central MET amplification testing results in Phase II Group 5, additional participants may be enrolled to ensure there are at least 10 in stage 1 and 30 in total MET amplified participants centrally confirmed by Novartis-designated laboratory.

Data from participants in Group 5 will be reviewed on an ongoing basis to monitor the safety and efficacy/lack of efficacy. Independent from the interim analysis, the enrollment into Stage 1 could be stopped (early) if there is a safety concern or evidence of lack of efficacy, defined as one of the following:

- No responders in the first 10 MET amplified (centrally confirmed) participants
- Onset of new brain metastasis in 2 participants
- 10 participants permanently discontinue capmatinib monotherapy before completion of the second tumor assessment because according to investigator judgement participants are not benefiting from capmatinib monotherapy treatment.

Participants will start the treatment with capmatinib monotherapy and may be followed with capmatinib in combination with nazartinib upon capmatinib monotherapy radiological disease progression based on investigator's assessment per RECIST 1.1.

Treatment can be continued with capmatinib in combination with nazartinib until radiological disease progression based on investigator's assessment per RECIST 1.1 or other reasons for treatment discontinuation as defined in the protocol in Section 7.1.4.

Group allocation will be managed by IRT.

In Phase II Group 5, MET amplification (GCN≥5) status can be determined per validated local laboratory, or central Novartis laboratory if local results not available. A mandatory biopsy sample collected any time after progression on prior line of EGFR TKI must be submitted at pre-screening or screening for confirmation of MET status and other biomarker analysis.

In all Phase II groups, an appropriate biopsy sample must be available for resistance mechanism analysis by a Novartis designated central laboratory. This biopsy sample should have been collected:

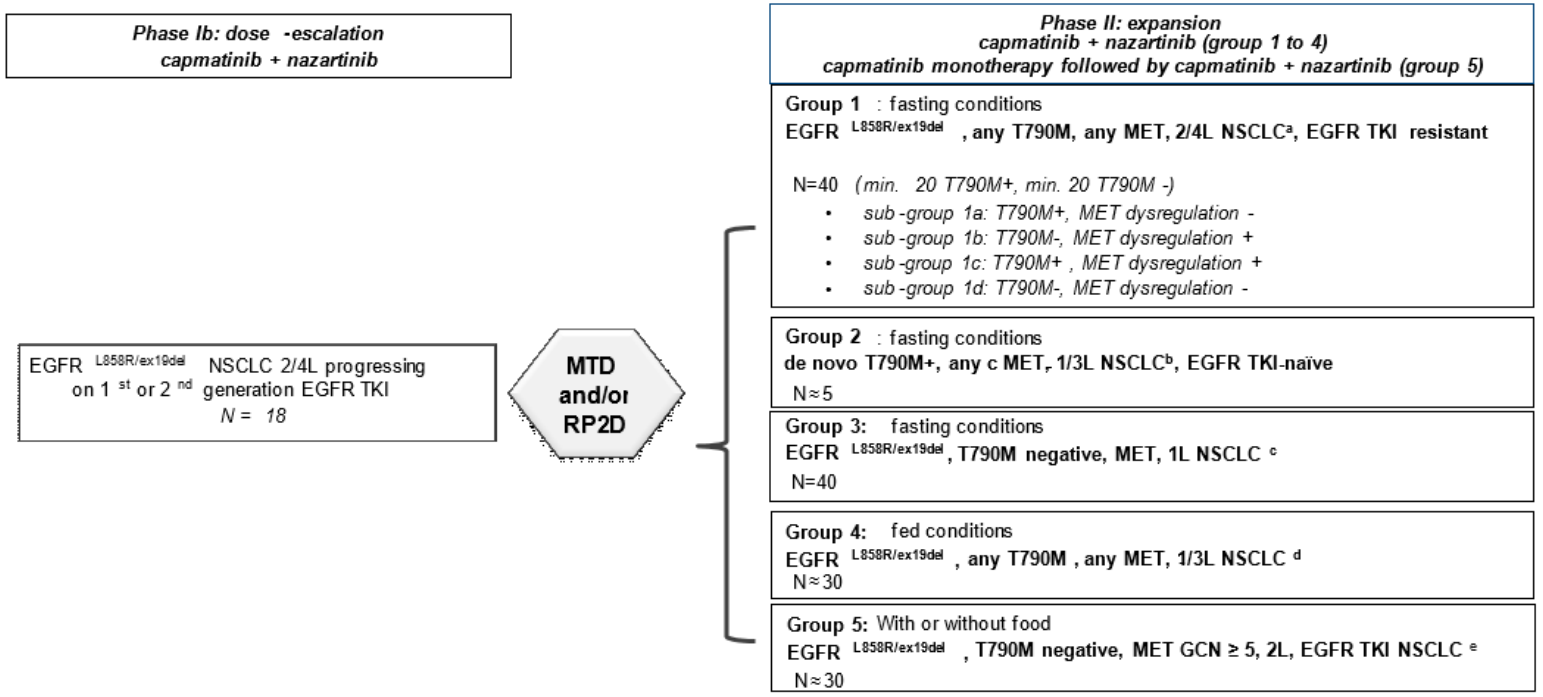
- At or any time after progression on the last treatment line by EGFR TKI in Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant) ;
- At any time in Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve) and Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic).
- At any time in treatment-naïve participants or at/or any time after progression on the last treatment line for advanced disease in Group 4 (EGFRmut, any T790M, any MET, 1/3L antineoplastic).

At or any time after progression on prior line of EGFR TKI for Group 5 (EGFRmut, any T790M, MET Gene Copy Number (GCN) ≥ 5, 2L antineoplastic, EGFR TKI resistant).

Details on sample size and operating characteristics are provided in Section 10.9.

Details of the biomarker collection plan are presented in Section 7.2.4.

Figure 4-1 Study design



a: 1 to 3 prior lines of systemic antineoplastic therapies in the therapeutic setting before study entry, including one line maximum of 1st or 2nd generation EGFR TKI

b: none to 2 prior lines of systemic antineoplastic therapies in the therapeutic setting before study entry without any line of therapy known to inhibit EGFR

c: no prior line of systemic antineoplastic therapies in the therapeutic setting before study entry (max one cycle of chemotherapy allowed)

d: none to max. 2 prior lines of systemic antineoplastic therapies in the therapeutic setting before study entry

e: max. 1 prior line of systemic antineoplastic therapies in the therapeutic setting before study entry, including one line maximum of 1st or 2nd generation EGFR TKI or osimertinib

1st and 2nd generation EGFR TKIs include but are not limited to: erlotinib, gefitinib, afatinib

A treatment is defined as a combination of medications, or single- agent medication, used to treat the disease indication. If the medication in a single agent treatment line or any of the medication (s) in combination therapy were interrupted due to reasons other than disease progression (for example, toxicity, physician's decision, etc.) and this was followed by re- challenge with the same medication or different 'substitute' medication(s), without evidence of progres sion, then all of these medications should be considered as a single treatment line.

Groups 1, 3 & 4: in the instances where central assessment of EGFR T790M and MET would fail despite sufficient tumor sample submitted to Novartis designated central laboratory, the patient will be able to enroll onto the screening and treatment phases under the status "unknown resistance mechanisms"

Group 5: At or any time after progression on prior line of EGFR TKI for Group 5 (EGFRmut, any T790M, MET Gene Copy Number (GCN) ≥ 5, 2L antineoplastic, EGFR TKI resistant)

Molecular pre-screening

- For both the Phase Ib and the Phase II Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant), Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic), Group 4 (EGFRmut, any T790M, any MET, 1/3L antineoplastic), and Group 5 (EGFRmut, T790M-, MET GCN≥5, 2L, EGFR TKI resistant) parts of the study, documented proof of the presence of either exon 19 deletion and/or L858R mutation (or other rare activating mutations that confer sensitivity to first and second generation EGFR TKI (e.g. L861Q, G719X, S768I)) in EGFR is required for all participants enrolled in the study. This could have been determined at any point prior to screening. EGFR activating mutation status is determined by a local laboratory. A laboratory report showing evidence of EGFR activating mutations must be available in the source documents. For participants harboring G719X mutations, a local report showing either the exact mutation type (G719A/S/C/U) or G719X is acceptable.
- Additionally for Phase Ib, MET dysregulation and $EGFR^{T790M}$ mutation testing should be performed locally or by the Novartis designated central laboratory on a newly obtained tumor sample or on an archival tumor sample obtained at or any time after progression on prior EGFR TKI therapy. $EGFR^{T790M}$ status can be determined locally utilizing:
  - In the United States: QIAGEN Therascreen EGFR RGQ PCR assay
  - In the other countries: either Roche Cobas or QIAGEN Therascreen test
  - If $EGFR^{T790M}$ status is not available locally or if it is available locally but determined by a test other than those outlined above, central assessment of $EGFR^{T790M}$ will be performed by a Novartis-designated central laboratory.
  - Local assessment of MET-amplification using fluorescence in situ (FISH) or immunohistochemistry (IHC) and assessed in a biopsy collected at or any time after the progression on prior EGFR TKI will be acceptable for study entry. Central assessment of MET amplification will be performed at a Novartis-designated central laboratory if MET molecular assessment is not available locally.
- For Phase II Group 1(EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant), $EGFR^{T790M}$ testing and MET dysregulation analysis must be performed by the Novartis designated central laboratory on a newly obtained tumor sample or on an archival tumor sample obtained at or any time after the last progression on prior EGFR TKI before study entry.
- For Phase II Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve) and Phase II Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic) $EGFR^{T790M}$ mutation testing and MET dysregulation analysis must be performed by the Novartis designated central laboratory on a newly obtained tumor sample or on an archival tumor sample collected at any time before study entry.
- For Phase II Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic) $EGFR^{T790M}$ mutation testing and MET dysregulation analysis must be performed by the Novartis designated central laboratory on a newly obtained tumor sample or on an archival tumor sample collected at any time before study entry (if treatment-naïve) or at/or any time after progression on last antineoplastic treatment (if 2/3L participants); **if biopsy is not available after last treatment, the most recent available archival biopsy**

should be provided.For Phase II Group 5 (EGFRmut, T790M-, MET GCN≥5, 2L, EGFR TKI resistant), in order to be considered eligible for the study, participants must have documentation of EGFR activating mutant and T790M negative NSCLC by a tissue-based test (for additional details see Section 5.2). The results from procedures performed as part of the local standard practices (prior to enrolling in the trial) will satisfy the inclusion criteria. If T790M testing is not available locally, confirmation of T790M status at a Novartis-designated central laboratory is required to confirm the participant's eligibility. In this case, the tumor sample provided should be indicated in the appropriate eCRF and requisition forms. Eligible participants must have MET amplification confirmed by either a validated local or central laboratory (Phase II Group 5 only, see Section 5.2) or a Novartis designated central laboratory (all other Phase II groups). For participants enrolled with local results, MET amplification will be retrospectively confirmed using a validated FISH test that detects MET amplification via DNA derived from formalin fixed, paraffin-embedded human tissue at the Novartis-designated laboratory.

All participants must sign the pre-screening consent to allow for the collection, and submission of tumor biopsy samples to the Novartis designated central laboratory for analysis, or to allow for anonymized local laboratory reports access as applicable.

Refer to Section 7.1.1 and Section 7.2.4 for further details.

Screening period

The screening period begins once the participant has signed the study informed consent. Participants will be evaluated against study inclusion and exclusion criteria and safety assessments (Table 7-1, Table 7-2 and Section 7.1.2).

Treatment period

The treatment period will begin on Cycle 1 Day 1. The study treatment will be administered in 28-days cycles.

30-day follow-up (FU) period

30 days after the last administration of study treatment, participants will be followed up for safety evaluations (Table 7-1, Table 7-2 and Section 7.1.6).

Disease progression FU

Participants who discontinue study treatment for any reason other than disease progression will be followed up for progression of disease (Section 7.1.6).

Survival FU

All participants, except participants from Phase II Group 5, will be followed for survival (Section 7.1.6).

4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned in the Phase Ib part of the study. However, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study (Section 6.2.3).

During the Phase II part, an interim analysis to assess futility is planned for Phase II Group 3 and Group 5. In addition, data from participants in the Phase II part will be reviewed on an ongoing basis to monitor the safety and tolerability of the MTD/RP2D.

Interim analysis for Phase II Group 3

During the Phase II part, an interim analysis to assess futility is planned on Phase II Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic) when approximately 20 participants have completed at least 4 cycles of treatment or discontinued treatment prior to that time.

Assessment of futility will be based on the calculated Bayesian probability of success (PoS). The Phase II Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic) will be stopped for futility if the PoS is less than 10% at the interim analysis.

If applicable, enrollment of participants into the Phase II Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic) will continue between the time the required data for participants in the interim analysis are observed and the time the results of the IA are available. Enrollment of participants into groups not evaluated in the interim analysis will also continue.

If futility is concluded, the enrollment of 1L participants (Group 3 and 1L participants in Group 4) may be stopped. Enrollment in opened groups with pre-treated participants will continue.

Detailed information on the statistical considerations for the interim analysis is provided in Section 10.8 and Section 10.9. The internal clinical trial team will perform the analysis and make the decision, as described in Section 8.5.

Interim analysis for Phase II Group 5

An interim analysis to assess futility is planned on Phase II Group 5 (EGFRmut, T790M-, MET GCN≥5, 2L, EGFR TKI resistant) when 10 participants have completed at least 2 tumor assessments while on treatment with capmatinib monotherapy and have been assessed as MET amplified (centrally confirmed), had radiological disease progression per RECIST 1.1 or discontinued treatment, whichever is earlier. The intent of this interim analysis is to be able to stop the enrollment if there is evidence of lack of efficacy (futility) of the capmatinib monotherapy. Recruitment will be on temporary halt while conducting the IA.

The decision to stop for futility at the interim will be based on the predictive probability (PP) of final observed ORR ≥ historical control ORR (35%) (Section 10.8) and will be calculated based on the actual number of evaluable participants at the interim analysis. The group will be stopped for futility if the respective PP is less than 1% at the interim analysis. With 10 evaluable participants for the interim analysis, if no response (CR or PR per RECIST 1.1 based on investigator assessment) is observed while the participants were on monotherapy, then Group 5 will be stopped for futility.

All evaluable participants at the time of the data cut-off for the interim analysis will be used to obtain the futility boundary using the PP criteria. The futility boundary will be calculated according to the actual number of evaluable participants in the interim analysis.

The statistical considerations for the interim analysis can be found in Section 10.8.

4.3 Definition of end of the study

The primary analysis will be conducted after all participants have completed 6 cycles (about 6 months of treatment) or all participants have permanently discontinued study treatment, whichever comes first. Due to the expected difference in enrollment completion for each group, the primary analysis for the different groups may occur at different times. The primary analysis/analyses data for participants in Phase Ib and Phase II Groups 1 to 4 has been summarized in the primary clinical study report (CSR) released in November 2019. The final analysis for participants in groups 1 to 4 will be included in an interim CSR.

The primary analysis for Group 5 will be performed when all participants in the group have completed at least 6 cycles of capmatinib monotherapy or discontinued capmatinib monotherapy prior to that time. If participants are ongoing at that time, a further final CSR might be prepared. This report will become the final CSR for the study. Following the cut-off date(s) for the analysis reported in the primary CSR(s), the study will remain open. Ongoing participants will continue to receive study treatment (capmatinib + nazartinib) and be followed as per the schedule of assessments, as long as participants derive benefit from the capmatinib + nazartinib combination.

The end of study is defined as the earliest occurrence of one of the following:

- All participants have died or discontinued from the study
- Futility/Lack of efficacy (only for Group 5 Stage 1, please refer to section 4.1)
- Another clinical study becomes available that can continue to provide capmatinib monotherapy or capmatinib in combination with nazartinib in this participant population and all participants ongoing are eligible to be transferred to that clinical study

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to participants who in the opinion of the Investigator are still deriving clinical benefit. Participants who continue to demonstrate clinical benefit will be eligible to receive study drug. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of the sponsor.

The sponsor reserves the right to terminate access to study drug if any of the following occur:

a) the marketing application is rejected by responsible health authority
b) the study is terminated due to safety concerns
c) the participant can obtain medication from a government sponsored or private health program
d) therapeutic alternatives become available in the local market

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Reasons for early termination:

- 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 drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should this be necessary, the participant should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.4 for a discontinued or withdrawn participant. 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 and/or ECs of the early termination of the trial.

5 Population

5.1 Study population

For the Phase Ib and the Phase II Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant), Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic), and Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic), adult participants with advanced or metastatic EGFR mutant L858R and/or ex19del NSCLC will be eligible (or other rare activating mutations that confer sensitivity to first and second generation EGFR inhibitors (e.g. L861Q, G719X, S768I)), whereas for Phase II Group 2 participants harboring a de novo $EGFR^{T790M}$ mutation will be eligible to participate in this study.

During the Phase Ib dose escalation part, participants who have progressed on first or second generation EGFR TKI treatment (e.g. gefitinib, erlotinib or afatinib) will be enrolled.

The Phase II Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant) will enroll participants who had a clinical benefit (complete response (CR)/PR any duration or stable disease (SD) for at least 6 months) on first or second generation EGFR TKI and subsequently progressed on this first or second generation EGFR TKI treatment. Participants should not have received more than one prior line of EGFR TKI and no more than three prior lines (including the EGFR TKI) of antineoplastic therapy for NSCLC. Participants in the Phase II part Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant) will be assigned according to their acquired resistance mechanism to four sub-groups:

a. sub-group 1a : $EGFRmut^{L858R/ex19del}$ NSCLC with acquired mutation T790M *(T790M+, MET dysregulation-)*
b. sub-group 1b : $EGFRmut^{L858R/ex19del}$ NSCLC with demonstrated MET dysregulation *(T790M-, MET dysregulation+)*. MET dysregulation is defined as either MET gene copy number ≥ 4 by FISH and/or IHC 3+ (defined as ≥50% of cells staining with high intensity).

c. sub-group 1c: EGFRmut$^{L858R/ex19del}$ NSCLC with evidence of both acquired T790M and MET dysregulation *(T790M+, MET dysregulation+)*
d. sub-group 1d: EGFRmut$^{L858R/ex19del}$ NSCLC with MET below the levels for sub-group b *(T790M-, MET dysregulation-)*.

In the Phase II part Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve), participants should not have received prior EGFR inhibitor treatment and no more than two prior lines of antineoplastic therapy for NSCLC.

In the Phase II Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic), participants should not have received any prior line of systemic antineoplastic therapy in the advanced setting (NSCLC stage IIIB or IV). However, participants who have received no more than 1 cycle of systemic antineoplastic therapy in the advanced setting are allowed.

In the Phase II Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic) participants, with documented EGFRmut NSCLC, who have never received any systemic antineoplastic therapy or have failed (defined as intolerance to treatment or documented disease progression) a maximum of 2 lines of antineoplastic therapies for advanced disease will be enrolled. Group 4 participants will take study drugs with food (unrestricted meal type).

In the Phase II Group 5 (EGFRmut, T790M-, MET GCN $\geq$ 5, 2L, EGFR TKI resistant), previously documented EGFR activating mutation (e.g., L858R and/or ex19del), T790M negative, MET amplified who have progressed on one prior line of therapy EGFR TKI for advanced/metastatic NSCLC disease will be given capmatinib monotherapy followed by capmatinib in combination with nazartinib.

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.

5.2 Inclusion criteria

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

1. Written informed consent must be obtained prior to any screening procedures.
2. Participants (male or female) $\geq$ 18 years of age.
3. Participants in Phase Ib and Phase II Groups 1 to 4 with histologically documented, locally advanced or recurrent (stage IIIB who are not eligible for combined modality treatment) or metastatic (Stage IV) non-small cell lung cancer.

   Participants in Phase II Group 5 must have stage IIIB/IIIC (not amenable to curative surgery, chemoradiation or radiation) or stage IV NSCLC at the time of study entry according to AJCC version 8.
4. Participants in Phase Ib and Phase II Groups 1 to 4 must have advanced NSCLC with locally documented EGFR^{L858R} mutation and/or ex19del (or other rare activating mutations that confer sensitivity to first and second generation EGFR inhibitors (e.g. L861Q, G719X, S768I), or a characterized de novo EGFR^{T790M} mutation).

   Biomarker requirements for participants in Phase II Group 5 are detailed in Inclusion criteria 15.
5. Presence of at least one measurable lesion according to RECIST 1.1 as per Appendix 1.

6. ECOG performance status ≤1
7. Participants must be screened for HBV. Participants who are either HBsAg positive or HBV-DNA positive must be willing and able to take antiviral therapy 1-2 weeks prior to first dose of study treatment (capmatinib+nazartinib) and continue on antiviral therapy for at least 4 weeks after the last dose of study treatment. Additional management of the participants would be provided by a physician with expertise in management of HBV, if needed.
8. Participants must be screened for HCV. Participants must have negative hepatitis C antibody (HCV Ab) or are HCV Ab positive but with an undetectable level of HCV-RNA. Note: participants with detectable HCV-RNA are not eligible for the study.
9. **For Phase Ib,** participants must have either an acceptable local result detailing their MET and $EGFR^{T790M}$ status in a biopsy collected at or post progression on the previous EGFR TKI therapy, or sufficient tumor material available from a biopsy collected at or post progression on prior EGFR TKI for central assessment of MET and $EGFR^{T790M}$. **For Phase II**, participants must have sufficient material available for results from central assessment of MET and $EGFR^{T790M}$. The biopsy must be collected at or post progression on last EGFR TKI treatment line for Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant) and Group 5 (EGFRmut, T790M-, MET GCN≥5, 2L, EGFR TKI resistant), at any time for Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve), Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic) and Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic).
10. **Phase Ib only:** documented progression of disease according to RECIST 1.1 while on continuous treatment with EGFR TKI (e.g. erlotinib, gefitinib or afatinib).
11. **Phase II Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant) only:** Participants demonstrated a documented clinical benefit (CR (any duration), PR (any duration), or SD for at least 6 months) on prior EGFR TKI (e.g. erlotinib, gefitinib or afatinib) and subsequently demonstrated progression according to RECIST 1.1.
12. **Phase II Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve) only:** Participants must have advanced NSCLC with a "de novo" T790M EGFR mutation:
    a. Participants must have NSCLC harboring a documented $EGFR^{T790M}$ mutation identified by the Novartis designated central laboratory. An archival or newly obtained tumor sample must be available for molecular pre-screening.
    b. For purposes of this protocol "de novo" T790M will be defined as the presence of $EGFR^{T790M}$ in NSCLC participants who have NOT been previously treated with any therapy known to inhibit EGFR.
13. **Phase II Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic) only:** participants must harbor an EGFR activating mutation and must be naïve from any line of systemic antineoplastic therapy in the advanced setting.
14. **Phase II Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic) only:** All participants must harbor an EGFR activating mutation and 2/3L participants must have failed (defined as intolerance to treatment or documented disease progression) a maximum of 2 prior lines of antineoplastic therapy in the advanced setting.

15. Phase II Group 5 (EGFRmut, T790M-, MET GCN≥5, 2L, EGFR TKI resistant) only:

- Histologically or cytologically confirmed diagnosis of NSCLC (excluding squamous cell carcinoma) with all the following:
    - EGFR mutations known to be associated with EGFR TKI sensitivity. This must be assessed as part of the participant standard of care by a validated test for EGFR mutations, as per local regulations. Exon 19 del, L858R, either alone or in combination with other EGFR sensitivity mutation assessed by a CLIA-certified USA laboratory or an accredited local laboratory outside the USA must be documented in the participant source documents before the participant can be consented for pre-screening for MET amplification status.
    - EGFR T790M negative status for participants who have progressed on first or second generation EGFR TKI, or third generation EGFR TKI other than osimertinib, as per tissue-based result from a CLIA-certified USA laboratory or an accredited local laboratory outside of the USA, by a validated test according to local regulations. Results must be documented in the participant source documents before the participant can be consented for pre-screening for MET amplification. If a local T790M result is not available, T790M status in tissue per central Novartis-desginated laboratory result is required.
    - MET gene amplification defined as: Gene copy number (GCN) ≥ 5 per tissue-based result from a CLIA-certified USA laboratory or an accredited local laboratory outside of the USA by a test that is validated according to local regulations with results documented in the participant source documents. An adequate amount of tumor tissue (archived or if not available, newly obtained biopsy sample) must be available at the time of enrollment for central assessment of MET gene amplification status. If a local result is not available, a tumor tissue sample must be submitted and determined as MET amplified (GCN ≥ 5) per central Novartis-designated laboratory.
    - Histological transformation from NSCLC into small cell lung cancer (SCLC) following previous EGFR TKI treatment are excluded.
- Participants must have progressed on one prior line of therapy either to first/second generation EGFR TKIs, osimertinib or other third generation EGFR TKIs for advanced/metastatic disease (stage IIIB/IIIC [not amenable to curative surgery, chemoradiation or radiation or stage IV NSCLC). Acquired resistance to EGFR TKI treatment is defined as documented clinical benefit (CR [any duration], PR [any duration], or SD for at least 6 months) on prior first/ second EGFR TKIs (e.g., erlotinib, gefitinib, afatinib, dacomitinib), osimertinib or other third generation EGFR TKI (such as almonertinib and furmonertinib) and subsequently demonstrated radiological disease progression. 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 systemic chemotherapies will count as one prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant or adjuvant systemic therapy. Adjuvant osimertinib therapy will count as prior line of EGFR TKI treatment if relapse occurs during the adjuvant osimertinib therapy.

16. Participants must have a life expectancy of at least 3 months.
17. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

5.3 Exclusion criteria

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

1. **Phase Ib:**
   - More than one previous treatment line with erlotinib, gefitinib or afatinib
   - Previous treatment with any investigational agent known to inhibit EGFR (mutant or wild-type)
   - Participants who have received more than three prior lines of antineoplastic therapies (including EGFR TKI) in advanced setting.
2. **Phase II:**
   - Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant):
     - More than three prior lines of systemic antineoplastic therapies (including EGFR TKI) in the advanced setting
     - More than one previous treatment line with first or second generation EGFR TKI (e.g. erlotinib, gefitinib, afatinib) in the advanced setting
     - Previous treatment with an investigational or marketed third generation EGFR TKI (e.g. osimertinib, CO-1686, nazartinib)
     - Previous treatment with other investigational or marketed agent known to inhibit EGFR (e.g. EGF monoclonal antibody therapy, dual TKI inhibitor)
   - Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve):
     - More than two previous treatment lines of systemic antineoplastic therapies in the advanced setting.
     - Previous treatment with an investigational or marketed agent that inhibits EGFR. EGFR inhibitors include (but not limited to) all generations of EGFR TKI (e.g. erlotinib, gefitinib, afatinib, osimertinib, CO-1686, nazartinib) or other anti-EGFR or EGFR monoclonal antibody therapy or dual TKI inhibitors.
   - Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic):
     - De novo EGFR T790M mutation identified by central assessment
     - Previous treatment with any systemic antineoplastic therapy in the advanced setting (NSCLC stage IIIB or IV). Participants who received only one cycle of systemic antineoplastic therapy in the advanced setting are allowed.
   - Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic):
     - More than two prior lines of systemic antineoplastic therapies in the advanced setting
     - Previous treatment with an investigational or marketed third generation EGFR TKI (e.g. osimertinib, CO-1686, nazartinib)
     - Previous treatment with an investigational or marketed agent that inhibits EGFR (e.g.: EGF monoclonal antibody therapy or dual TKI inhibitors).

For participants in Group 1 to 4, systemic antineoplastic therapy administered as adjuvant or neo-adjuvant treatment more than six months prior to study enrollment is not considered a prior line of therapy for purpose of this study. For participants in Group 5, please refer to inclusion criteria 15.

3. Previous treatment with a MET inhibitor or HGF-targeting therapy.
4. Participants with symptomatic brain metastases. However, participants with asymptomatic/controlled brain metastases may participate in the trial. If treatment is required, these participants must have completed any planned radiation therapy and/or surgery > 2 weeks prior to the first dose of study treatment and remain asymptomatic. Participants must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on central nervous system imaging. Participants taking steroids must have been on a stable dose for two weeks prior to the first dose of study treatment.

For Group 5: Participants with symptomatic CNS metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms. 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.

5. Any medical condition that would, in the investigator's judgment, prevent the participant's participation in the clinical study due to safety concerns or compliance with clinical study procedures (e.g., active infection, inflammation, intestinal obstruction, unable to swallow medication, social/psychological issues, etc.). Any severe, acute, or chronic medical or psychiatric condition or laboratory abnormality or substance abuse that may increase the risk associated with study participation or study treatment administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for the study.
6. Presence or history of another malignancy.

Exception: Participants who have been disease-free for 3 years, or participants with a history of adequately treated in-situ carcinoma of the uterine cervix, completely resected basal or squamous cell carcinoma, non-melanomatous cancer of skin, history of stage IA melanoma that has been cured, are eligible.

For Group 5: 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.

7. Undergone a bone marrow or solid organ transplant.
8. Known history of human immunodeficiency virus (HIV) seropositivity (HIV testing is not mandatory).

For Group 5: Participants with known history of testing positive for human immunodeficiency virus (HIV) infection, and with a history of acquired immunodeficiency syndrome (AIDS)-defining 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. HIV participants coinfected with hepatitis virus 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.

9. Participants receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry except for control of brain metastases, topical applications, inhaled sprays, eye drops or local injections.
10. Participants with clinically significant, uncontrolled cardiovascular disease, such as:
    - Unstable angina within 6 months prior to screening
    - Myocardial infarction within 6 months prior to screening
    - Participants with a history of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Participants with uncontrolled hypertension defined as a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening
    - Ventricular arrhythmias
    - Supraventricular and nodal arrhythmias not controlled with medication
    - Other cardiac arrhythmia not controlled with medication
    - Participants with corrected QT (QTc) ≥470 ms using Fridericia correction (QTcF) on the screening ECG (using the average QTcF of the triplicate ECGs)
11. 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).
12. Unable or unwilling to swallow tablets or capsules.
13. Participants have received anti-cancer therapies within the following time frames prior to the first dose of study treatment:
    - Conventional cytotoxic chemotherapy: ≤4 weeks (≤6 weeks for nitrosoureas and mitomycin-C)
    - Biologic therapy (e.g., antibodies): ≤4 weeks
    - Non-cytotoxic small molecule therapeutics: ≤5 half-lives (if half-life known) or ≤2 weeks
    - Other investigational agents: ≤4 weeks
    - For Group 5: Previous anti-cancer and investigational agents within 4 weeks or ≤ 5 x half-life of the agent (whichever is shorter) before first dose of capmatinib. If previous treatment is a monoclonal antibody, then the treatment must be discontinued at least 4 weeks before first dose of capmatinib. If previous treatment is an oral targeted agent, then the treatment must be discontinued at least 5 x half-life of the agent.
    - For Group 5: Treatment with a prior first or second generation EGFR TKIs (e.g., erlotinib, gefitinib, afatinib, dacomitinib), osimertinib or another third generation EGFR TKIs within 14 days or approximately 5x half-life, whichever is shorter, of the first dose of study treatment (if sufficient washout time has not occurred due to schedule or PK properties, an alternative appropriate washout time based on known duration and

time to reversibility of drug related adverse events could be agreed upon by Novartis and the Investigator).

14. Participants who have received thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or participants who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤ 2 weeks prior to starting the study treatment or participants who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment.
15. Major surgery: ≤2 weeks.

    For Group 5: Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting capmatinib or who have not recovered from side effects of such procedure. 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.
16. Participants (except those in Phase II Group 5) have not recovered from all toxicities related to prior anticancer therapies to grade ≤1 (CTCAE v 4.03). Participants in Phase II Group 5 will use version 5.0. Participants with any grade of alopecia are allowed to enter the study.
17. **Participants in Phase Ib and Phase II Groups 1 to 4** have out of range laboratory values defined as:
    - Absolute Neutrophil Count (ANC) <1.5 x 10^9/L (1.5 x 10^3/μL)
    - Hemoglobin (Hgb) <9 g/dL (90 g/L)
    - Platelets (PLT) <75 x 10^9/L (75 x 10^3/μL)
    - Total bilirubin >1.5 x upper limit of normal (ULN)
    - AST and/or ALT >3 x ULN, except for participants with liver metastasis who may not be included if AST and/or ALT >5 x ULN
    - Alkaline phosphatase (ALP) >5 xULN
    - Calculated creatinine clearance < 45mL/min (0.75 mL/sec) using Cockcroft-Gault formula
    - Asymptomatic serum amylase or lipase > Grade 2
    - Serum amylase or serum lipase CTCAE grade ≥ 1 with signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g. elevated P-amylase, abnormal imaging findings of pancreas, etc.)

Participants in Phase II Group 5 have out of range laboratory values defined as:

- Absolute Neutrophil Count (ANC) <1.5 x 10^9/L (1.5 x 10^3/μL) without growth factor support
- Hemoglobin (Hgb) <9 g/dL (90 g/L)
- Platelets (PLT) <100 x 10^9/L (100 x 10^3/μL)
- Total bilirubin >1.5 x upper limit of normal (ULN)
- AST and/or ALT > 2.5 x ULN except for participants with liver metastasis, who may not be included if AST and/or ALT > 5 x ULN
- Alkaline phosphatase (ALP) >5 xULN

- Calculated creatinine clearance (using Cockcroft-Gault formula) < 50 mL/min
- Asymptomatic serum amylase increase grade 1 and 2 are allowed if at the beginning of the study is 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

18. Participants have the following laboratory values outside of the laboratory normal limits or cannot be corrected to within normal limits with supplements during screening:
    - Potassium
    - Magnesium
    - Phosphorus
    - Total calcium (corrected for serum albumin)
19. Participants receiving treatment with medications that are known to be:
    - strong inhibitors or inducers of CYP3A4/5,
    - or CYP3A4/5, CYP1A2, CYP2C8, CYP2C9, CYP2C19, and/or CYP2D6 substrates with narrow therapeutic index,
    - or at risk for QT interval prolongation and/or Torsades de Pointe (long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome),
    - and cannot be discontinued or replaced by safe alternative medication within 5 half-lives or 7 days prior (whichever is longer) to the start of study treatment and for the duration of the study.
    - For Phase II Group 5 (capmatinib monotherapy): strong inducers of CYP3A that cannot be discontinued at least 1 week prior to the start of treatment with capmatinib and for the duration of the study.
    - Please refer to Appendix 4 for a list of prohibited concomitant medications.
20. Participants who have impairment of GI function or GI disease that may significantly alter the absorption of study treatment (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome)
21. Pregnant or nursing (lactating) women.
22. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months after stopping the study treatments. 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 sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male partner: 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, 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 childbearing 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 ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

23. Sexually active males unwilling to use a condom during intercourse while taking drug and for 3 months after stopping investigational medications. 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.
24. Participants with known hypersensitivity or contraindications to capmatinib or nazartinib, or any excipient of these agents.
25. For Group 5: Carcinomatous meningitis.
26. For Group 5: Known EGFR T790M positive, Known C797S positive, known druggable molecular alterations (such as ROS1, BRAF, KRAS etc.) who might be candidates for alternative targeted therapies as applicable per local regulations and treatment guidelines.
27. 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

The investigational drugs to be used in this study are nazartinib and capmatinib.

The study treatment is the combination of nazartinib (once a day) and capmatinib (twice a day).

In Phase II Group 5, the participants will start with capmatinib monotherapy (twice a day) and then will have the opportunity to continue with the combination of nazartinib (once a day) and capmatinib (twice a day) based on radiological disease progression evaluation based on investigator’s assessment per RECIST 1.1.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration*	Dose strengths*	Frequency and/or Regimen
Nazartinib	Capsule for oral use	25 mg, 50 mg, 100 mg	Daily
Nazartinib	Tablet for oral use	25 mg, 50 mg, 200 mg	Daily
Capmatinib	Tablet for oral use	100 mg, 150 mg, 200 mg	Twice daily
* For participants in Phase II Group 5, nazartinib will only be available in capsule for oral use with the dose strengths of 25 mg and 50 mg. Capmatinib will only be available in tablet for oral use with the dose strengths of 150 mg and 200 mg.			

In the Phase Ib part of the study, the starting dose for the first cohort of participants will be 50 mg q.d. for nazartinib and 200 mg b.i.d. for capmatinib.

Note: on 23-Feb-2016, RP2D was declared during the 5th dose-escalation teleconference during the Phase Ib part of the study. In the Phase II for Groups 1 to 4, all participants will receive the RP2D, i.e. **capmatinib 400 mg b.i.d. + nazartinib 100 mg q.d**.

In the Phase II part of the study, participants of Group 5 will start with capmatinib 400 mg b.i.d monotherapy. Upon radiological disease progression based on investigator's assessment per RECIST 1.1, Nazartinib 100 mg q.d. will be administered in the combination therapy together with capmatinib administered at the same dose with given during the monotherapy period.

Capmatinib and nazartinib will be supplied as open label participant specific supply.

Participants will be instructed to take the daily doses of capmatinib and nazartinib concurrently in the early morning, at approximately the same time each day. The second (evening) dose of capmatinib should be taken 12 ±2 hours apart from first dose (morning) of capmatinib.

Unless otherwise instructed, each dose of capmatinib and nazartinib shall be taken in the fasted state, at least one hour before or two hours after a meal (except Phase II Group 4 and Group 5). Participants will self-administer the study medication with a glass of water (approximately 250 mL) at about the same time every day. Nazartinib capsules should not be opened and study medication (nazartinib and capmatinib) should be swallowed whole and not chewed. During the fasting period, participants are free to drink water. On the days when PK blood samples are to be collected (Section 7.2.3), participants will be instructed to hold their dose of study drugs and the administration of study drugs will be supervised by the study personnel.

For participants in Phase II Group 4, each dose of capmatinib and nazartinib should be taken within 30 minutes following a meal (unrestricted meal type). On the days when PK blood samples are to be collected, participants will be instructed to hold their dose of study drugs and come to the clinic fasting. The study drugs will be administered within 30 minutes following the meal with the supervision by the study personnel.

For participants in Phase II Group 5, each dose of capmatinib monotherapy or capmatinib plus nazartinib 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). Capmatinib and capmatinib plus nazartinib can be administered with or without food. Participants must be instructed to swallow the tablets whole and not to chew or crush them or dissolve them in water. Participants should take the recommended dose of capmatinib tablets

twice daily (b.i.d.) at approximately the same time each day starting at Cycle 1 Day 1. The morning and the evening doses should be taken 12 (± 4) hours apart, although a 12-hour interval is highly recommended.

On the days when samples for full PK profiles are taken (C1D1, C1D15 and C2D1 for all participants in Phase Ib and, C1D1 and C2D1 for the ten first participants in Phase II Group 3 and approximately twenty participants in phase II Group 4 as described in Section 7.2.3), the time of the meal before and after the dose needs to be recorded on the eCRF.

Participants must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos, pomegranate (and juice) and star citrus fruits at least 7 days prior to the first dose of study treatment and during the entire study treatment period due to potential CYP3A interaction. Regular orange juice is allowed.

Participants should be instructed not to make up missed doses. A missed dose is defined as any time point when a participant forgets to take capmatinib or nazartinib within 4 hours of the planned time of dosing, or if a participant forgets to take his/her dose for that day. In such cases, the dose should be omitted and the participant should continue treatment with the next scheduled dose.

If vomiting occurs, no attempt should be made to replace the vomited dose. If any episodes of vomiting occurred within the first 4 hours of capmatinib and nazartinib dosing on post dose PK sampling days, it must be noted in the Adverse Events CRF and the exact time of vomiting should be recorded on the appropriate Dosage Administration Record eCRF.

During the whole duration of the treatment with capmatinib in combination with nazartinib, the participant is recommended to use precautionary measures against ultraviolet exposure (refer to Section 6.3.3, Table 6-13).

6.1.2 Treatment duration

Participant may continue treatment with the study treatment until participant experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent/opposition to use data/biological samples. Refer to Section 7.1.3, Section 7.1.4 and Section 7.1.5.

Note: the study treatment may be continued beyond RECIST 1.1 defined progressive disease and until the end of the study as defined in Section 4.3 if, in the judgment of the investigator, there is evidence of clinical benefit and the participant wishes to continue with the study treatment. The judgment of the investigator should be documented in the Case Report Form and the continued evidence of clinical benefit should be updated on a regular basis. These participants will continue assessments as outlined in the assessments section and will complete the EOT visit only after permanent discontinuation from study treatment.

For Phase II Group 5: The treatment duration consists of a capmatininb monotherapy stage and an extension stage which is a combination treatment by adding nazartinib onto capmatinib. When participants progress on the capmatinib monotherapy, they will have the opportunity to enter the extension stage or persue alternative treatment which is in the best interest of participants.

If eligible and at the discretion of the Investigator, after capmatinib monotherapy radiological disease progression based on investigator's assessment per RECIST 1.1, participants will have the option to be followed with capmatinib in combination with nazartinib and must follow study assessments as per visit schedule in Table 7-2 in the combination treatment phase.

Participants must sign the combination treatment informed consent form (ICF) that details the associated risks capmatinib in combination with nazartinib therapy and additional assessments prior to starting the combination therapy.

For participants who progressed on the combination treatment, they will be permitted to continue the combination treatment as clinical data indicate that participants may derive benefit from continuing combination treatment despite initial evidence of disease progression. The judgment to continue treatment beyond progression from the investigator should be documented in eCRF with provision of 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 written consent to continue on the study treatment
- No new antineoplastic therapy has been initiated

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 from the study.

6.2 Dose escalation guidelines for the Phase Ib part

6.2.1 Starting dose rationale

The starting dose for capmatinib is set at 200 mg b.i.d. p.o. administered continuously. The rationale for the capmatinib starting dose is described in Section 2.3.

The selected starting dose for nazartinib in this study is 50 mg q.d. p.o.

Formulation change from nazartinib capsule to tablet

An immediate release film-coated tablet will be introduced during the study.

[redacted]

[redacted] The dissolution profile of the nazartinib tablet formulation was comparable or slightly slower than the dissolution profile for nazartinib capsule. Therefore, the exposure of nazartinib following the same dose of tablet administration is predicted to be comparable or lower than that for the capsule formulation.

The BLRM will be constructed for the nazartinib tablet formulation in combination with capmatinib. The cumulative dose-DLT data from the existing cohorts using nazartinib capsules in this study as well as those from the single agent studies of capmatinib and nazartinib will be incorporated into the model (seeAppendix 2, Section 14.2.3). The selected starting dose of nazartinib tablet formulation in combination with capmatinib must satisfy the following conditions:

- it should be a dose level that has already been tested in the nazartinib capsule formulation and satisfies the EWOC;
- it should satisfy the EWOC based on the estimation with the BLRM of the tablet formulation.

In the scenario that MTD/RP2D is already declared for the capsule formulation, the dose escalation for the tablet formulation will continue starting from the dose that satisfies all conditions mentioned above. This starting dose may or may not be the same as the MTD/RP2D of the capsule formulation. The MTD/RP2D for the tablet formulation will be declared separately following the same procedure described in Section 6.2.3.

6.2.2 Provisional dose levels

Table 6-2 and Table 6-3 describe the starting dose and the provisional dose levels of nazartinib and capmatinib, respectively, which may be evaluated during this trial. Dose escalation will continue until MTD is reached and/or RP2D of the nazartinib + capmatinib combination is determined. **Only one of the two investigational drugs can be escalated at a time.**

At all decision time points, the adaptive BLRM permits alterations in the dose increments based on the observed DLTs.

Table 6-2 Provisional dose levels for nazartinib

Dose level	Nazartinib proposed daily dose*	Increment from previous dose
-1**	25 mg	-
1 (starting dose for capsule formulation)	50 mg	-
2	100 mg	100%
3	200 mg	100%
4	400 mg	100%

*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts may be added at any time during dose escalation and at any dose level below either the estimated MTD or the RP2D for which safety data exists in order to better understand safety or PK.

**Dose level −1 represents a treatment dose for participants requiring a dose reduction from the starting dose level with nazartinib capsules.

Table 6-3 Provisional dose levels for capmatinib

Dose level	Capmatinib proposed dose*	Increment from previous dose
-1**	100 mg b.i.d.	-
1 (starting dose with nazartinib capsules)	200 mg b.i.d.	-
2	400 mg b.i.d.	100%
3	600 mg b.i.d.	50%
*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts may be added at any time during dose escalation and at any dose level below either the estimated MTD or the RP2D for which safety data exists in order to better understand safety or PK. **Dose level −1 represents a treatment dose for participants requiring a dose reduction from the starting dose level in combination with nazartinib capsules.		

6.2.3 Guidelines for dose escalation and determination of MTD/RP2D

6.2.3.1 MTD definition

The MTD is defined as the highest combination drug doses expected to cause DLT in less than 35% of the treated participants in the first cycle of treatment during the escalation part of the study. AEs and laboratory abnormalities considered to be DLTs are defined in Table 6-4. Since several combinations may correspond to this definition, more than one MTD may be identified with different doses of the study drugs. One of these MTDs or a lower dose combination will then be selected as the RP2D.

The applied adaptive Bayesian methodology provides an estimate of the combinations of nazartinib and capmatinib not exceeding the MTD. Typically the MTD is a tested combination with maximum probability of targeted toxicity (DLT rate between 16% and <35%). The use of the EWOC principle limits the risk that a potential next dose will exceed the MTD (Section 10.4.2).

6.2.3.2 Dose cohort modification

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled participants who will be treated at the specified dose level. The first cohort will be treated with the starting dose of nazartinib 50 mg q.d. in combination with capmatinib at the starting dose of 200 mg b.i.d.

Participants must complete a minimum of one cycle of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions (Section 10.1.4). Dose escalation decisions will occur when the cohort of participants has met these criteria. Dose escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade $\geq$ 2 toxicity data during Cycle 1 and PK data from evaluable participants. The recommended dose for the next cohort of participants will be guided by the Bayesian logistic regression model (BLRM) with EWOC principle (Section 2.2). The adaptive Bayesian methodology provides an estimate of all dose levels of nazartinib and capmatinib that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will

fall in the target interval [16-35%) and will always satisfy the EWOC principle. In all cases, the dose for the next cohort will not exceed a 100% increase from the previous dose. Smaller increases in dose may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data. Any dose escalation decisions made by investigators and Novartis personnel will not exceed the dose level recommended by the BLRM using the EWOC principle. If needed to better define the dose-toxicity relationship additional participants may be enrolled to the current dose level, to a preceding dose level, or to an intermediate dose level before proceeding with further dose escalation.

If two participants in a previously untested dose level experience a DLT, enrollment to that cohort will stop, the BLRM will be updated and the next cohort will be opened at the next lower dose level or an intermediate dose level that satisfies the EWOC principle (Table 14-11, Appendix 2). However, if two participants in a new cohort at a previously tested dose level experience a DLT (e.g., a total of eight participants are treated on this dose level with two DLTs observed), further enrollment to that cohort will stop, the BLRM will be updated with this new information and re-evaluation of the available safety and PK data will occur. By incorporating information gained at the preceding dose cohorts, additional participants may be enrolled into the current dose cohort only if the combination still meets the EWOC principle and as agreed by Investigators and Novartis personnel. Alternatively, if recruitment to the same cohort may not resume, a new cohort of participants may be recruited to a lower dose level as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk for this lower dose level to exceed the MTD remains below 25% (EWOC). Re-escalation may then occur if data in subsequent cohorts supports this (EWOC principle is satisfied) and Investigators and Novartis personnel agree.

Dose escalation will continue until identification of the MTD or a suitable lower dose for the Phase II part. This will occur when the following conditions are met:

- at least six participants have been treated at this dose
- this dose satisfies one of the following conditions:
  - the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
  - minimum of 18 participants have already been treated on the trial.
- it is the dose recommended for participants, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference, see Section 6.2.3.1.

To better understand the safety, tolerability and PK of nazartinib in combination with capmatinib, additional cohorts of participants may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

If a decision is made to escalate to a higher dose level but one or more additional participant(s) treated at the preceding dose level experiences a DLT during the first cycle of treatment, then the BLRM will be updated with this new information before any additional participants are enrolled at that higher dose level. Participants ongoing will continue treatment at their assigned dose levels.

Change of drug formulation for nazartinib:

For the first cohort with nazartinib tablets, data from all the previous cohorts will be down weighted (see Appendix 2, Section 14.2.3) and the BLRM will be run to get the starting dose for the new drug variant. Whatever the recommendation from the model is, this starting dose should never be higher than the doses that have already been used.

In the scenario when the MTD/RP2D is already declared for the dose combination with nazartinib capsules at the time of introduction of nazartinib tablets, the nazartinib tablet will be introduced at a dose level which was previously tested in the current study, which satisfies the EWOC criterion when the BLRM is run for tablet formulation and which is considered to be a safe dose to start with after reviewing all available safety and pharmacokinetic data from the current study as well as the single agent studies involving these two compounds. In this case there are two possibilities. The starting dose for the first cohort with nazartinib tablets will be either the MTD/RP2D for the capsule formulation or a lower dose level as described in Section 6.2.1.

6.2.3.3 Implementation of dose escalation decisions

To implement dose escalation decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

6.2.3.4 Intra-participant dose escalation

Intra-participant dose escalation is not permitted at any time within the first four cycles of treatment. After the forth cycle is completed, individual participants may be considered for treatment at a dose of nazartinib or capmatinib higher than the dose to which they were initially assigned. Only one of the investigational study drugs will be escalated at any one time. In order for a participant to be treated at a higher dose of nazartinib or capmatinib, he or she must have tolerated the lower dose for at least four cycles of therapy (i.e. he or she must not have experienced at the lower dose originally assigned a toxicity of CTCAE grade ≥ 2 for which the relationship to study treatment cannot be ruled out). Moreover, the new, higher dose with which the participant is to be treated must be a dose pair that has completed evaluation in a dose-escalation meeting and has not exceeded the MTD estimated by the Bayesian model given all available data.

There is no limit to the number of times a participant may have his or her dose of either nazartinib or capmatinib increased. In any further escalation, again only one study drug will be increased at any time. Any further increases after the initial intra-participant dose escalation are participant to the same rules as for the initial intra-participant escalation. Consultation and agreement with Novartis must occur prior to any intra-participant dose escalation occurring. These changes must be recorded on the Dosage Administration Record eCRF.

6.2.4 Definitions of dose limiting toxicities

A DLT is defined as an AE or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with nazartinib in combination with capmatinib during the escalation part of the study and meets any of the criteria included in Table 6-4. National Cancer Institute (NCI) CTCAE version 5.0 will be used for all grading. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling participants into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all participants at the current dose level.

Table 6-4 Criteria for defining dose-limiting toxicities in the Phase Ib part

Toxicity	Any of the following criteria:
Hematology	Any hematologic toxicity = grade 3, lasting for > 7 consecutive days
	Any hematologic toxicity ≥ grade 4 (of any duration)
	Febrile neutropenia (ANC < 1.0 x 10^9/L or 1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour.
Renal	Serum creatinine ≥ grade 3 (≥ 3.0 x baseline or > 3.0 - 6.0 x ULN)
Hepatic	Total bilirubin ≥ grade 3 (> 3 x ULN)
	AST or ALT = grade 3 (>5.0-20.0 x ULN) for >7 consecutive days AST or ALT = grade 4 (>20.0 x ULN)
	For participants with normal baseline AST and ALT and total bilirubin value: AST or ALT >3.0xULN combined* with total bilirubin >2.0 x ULN without evidence of cholestasis** OR For participants with abnormal baseline AST or ALT or total bilirubin value: [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 xULN], whichever is lower, combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN]
Pancreas	Asymptomatic serum amylase or lipase grade 3 (>2.0 – 5.0 × ULN) occurring for > 14 consecutive days Asymptomatic serum amylase or lipase grade 4 (>5.0 x ULN) of any duration
	Symptomatic serum amylase or lipase elevation, medical intervention required
Neurologic	Any neurological abnormality or toxicity ≥ grade 2
Diarrhea	≥ grade 3 despite optimal treatment
Skin and subcutaneous tissue disorders	≥ grade 3 despite 7 consecutive days of optimal treatment
Respiratory	≥ grade 2 pneumonitis or interstitial lung disease (ILD) without infection etiology
Other adverse events	Any adverse event ≥ grade 3 Single event or multiple occurrences of the same event that lead to a dosing interruption of > 7 days in Cycle 1, may be considered to be DLTs by the Investigators and Novartis, even if not CTCAE grade 3 or higher

Toxicity	Any of the following criteria:
* "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold ** "Cholestasis" defined as: ALP elevation >2xULN and R value (ALT/ALP in x ULN) < 2] in participants without bone metastasis, or elevation of ALP liver fraction in participants with bone metastasis) CTCAE version 4.03 will be used for all grading. Participants may receive supportive care (e.g. transfusion of red blood cells) as per local institutional guidelines.	

6.3 Dose modifications for toxicities

6.3.1 Dose modification and dose interruption

For participants who do not tolerate the protocol-specified dosing schedule due to drug related toxicities, dose interruptions and/or reductions are recommended in order to allow participants to continue the study treatment. For the dose escalation part of the study, dose reductions during cycle 1 are only allowed if a DLT is observed and recorded.

Table 6-7 provides recommendations for dose modification and dose interruption (i.e., interruption and re-initiation criteria for nazartinib and capmatinib treatment).

Refer to Table 6-5 and Table 6-6 for recommended dose reduction steps for the Phase II part of the study.

If, due to study drug related toxicity, a participant requires a dose interruption of >21 days from the intended day of the next scheduled dose, then the participant must be discontinued from the study treatment unless described otherwise.

Each participant is only allowed two dose reductions on each drug. In addition, a participant must discontinue treatment with nazartinib and capmatinib if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity.

Exceptions on dose interruptions and modifications can be made on a case by case basis after discussion with Novartis and Investigator.

In exceptional cases, after discussion with Novartis, participants may be allowed to continue treatment or resume treatment with only one of the investigational drugs.

All dose interruptions or modifications must be recorded on the Dosage Administration Record CRF.

In case of study treatment interruption, visit schedule should still be followed and assessments performed as per Table 7-1 and Table 7-2.

After dose modification, re-escalation to a previous dose level is not permitted apart from the exceptional cases described in Table 6-14 and Table 6-15.

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

Table 6-5 Dose reduction steps for capmatinib

Dose level	Proposed daily dose of capmatinib
0	capmatinib 400 mg b.i.d.
-1	capmatinib 300 mg b.i.d.
-2	capmatinib 200 mg b.i.d.

Table 6-6 Dose Reduction steps for nazartinib

Dose level	Proposed daily dose of nazartinib
0	nazartinib 100 mg q.d.
-1	nazartinib 75 mg q.d.
-2	nazartinib 50 mg q.d.
Note: dose reduction should be based on the worst toxicity demonstrated at the last dose	

Table 6-7 Criteria for dose reduction, interruption and re-initiation of nazartinib and capmatinib for adverse drug reaction

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
HEMATOLOGICAL	
Neutrophil count decreased (ANC) Neutropenia	
Grade 1 (ANC < LLN - 1500/mm^3; < LLN - 1.5 x 10^9/L)	Maintain dose levels of nazartinib and capmatinib
Grade 2 (ANC < 1500 - 1000/mm^3; < 1.5 - 1.0 x 10^9/L)	Maintain dose levels of nazartinib and capmatinib
Grade 3 (ANC <1000 – 500/mm^3)	Omit study treatment until resolved to ≤ grade 2, then resume nazartinib at the same dose level: • If fully resolved in ≤ 7 days, then resume capmatinib at same dose level • If fully resolved in > 7 days, then resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 toxicity on maintained dose of nazartinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 2, then resume nazartinib at↓ 1 dose level and the same dose level of capmatinib (i.e., both study drugs ↓ 1 dose level from dose levels at initial occurrence of grade 3 AE) • If recurrence of grade 3 during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 2, then resume nazartinib at↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy at ↓ 1 dose level, resume capmatinib at same dose level
Grade 4 (ANC < 500/mm^3)	Omit study treatment until resolved, then resume nazartinib at the same dose level • If no recurrence of grade 3 or higher toxicity after 7 days of nazartinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 or higher toxicity on maintained dose level of nazartinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 2, then resume nazartinib at↓ 1 dose level and capmatinib at the same dose level (i.e., both study drugs ↓ 1 dose level from levels at initial occurrence of grade 4 AE) • If recurrence of grade 3 or higher toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 2, then resume nazartinib at↓ 1 dose level • If no recurrence of grade 4 toxicity after 7 days of nazartinib monotherapy at↓ 1 dose level, resume capmatinib at the same dose level
Febrile Neutropenia	
ANC < 1000/mm3 and a single temperature of >38.3°C (101°F) or a sustained temperature of >=38°C (100.4°F) for more than one hour	Omit study treatment until resolved, then resume nazartinib at the same dose level: • If resolved in ≤ 7 days, resume capmatinib treatment at ↓ 1 dose level • If resolved in > 7 days, permanently discontinue capmatinib treatment • If recurrence during nazartinib monotherapy, omit nazartinib until resolved, then resume nazartinib ↓ 1 dose level and capmatinib at ↓ 1 dose level
Platelet count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75,000/mm3; < LLN - 75 x 10^9/L)	Maintain dose levels of nazartinib and capmatinib
Grade 2 (PLT < 75,000 - 50,000/mm3; < 75 - 50 x 10^9/L)	Maintain dose levels of nazartinib and capmatinib
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Omit study treatment until resolved to ≤ grade 2, then resume nazartinib at the same dose level:

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	• If fully resolved in ≤ 7 days, then resume capmatinib at same dose level • If fully resolved in > 7 days, then resume capmatinib ↓ 1 dose level • If recurrence of grade 3 toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 2, then resume nazartinib ↓ 1 dose level, resume capmatinib at same dose level
Grade 4 (PLT < 25,000/mm^3)	Omit study treatment until resolved to ≤ grade 2, then resume nazartinib at the same dose level: • If no recurrence of grade 3 or higher toxicity after 7 days of nazartinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 or higher toxicity on maintained dose of nazartinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 2, then ↓ 1 dose level of nazartinib and maintain dose level of capmatinib (i.e., both study drugs ↓ 1 dose level from dose levels at initial occurrence of grade 4 AE) • If recurrence of grade 3 or higher toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 2, then resume nazartinib ↓ 1 dose level • If no recurrence of grade 3 or higher toxicity after 7 days of nazartinib monotherapy at ↓ 1 dose level, resume capmatinib at ↓ 1 dose level
Hemoglobin decreased (Anemia)	
Grade 1 (Hgb < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L)	Maintain dose levels of nazartinib and capmatinib
Grade 2 (Hgb < 10.0 - 8.0 g/dL; < 6.2 – 4.9 mmol/L; < 100 - 80 g/L)	Maintain dose level of nazartinib and capmatinib
Grade 3 (Hgb < 8 g/dL)	Omit study treatment until resolved to ≤ grade 2, then resume at same dose levels of nazartinib: • If fully resolved in ≤ 7 days, then resume capmatinib at same dose level • If fully resolved in > 7 days, then resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 toxicity during nazartanib monotherapy, omit study treatment until resolved to ≤ grade 2, then resume nazartinib ↓ 1 dose level and resume capmatinib at same dose level
Grade 4 (life-threatening consequences; urgent intervention indicated	Omit study treatment until resolved to ≤ grade 2, then resume same dose level of nazartinib and re-evaluate in 7 days, or sooner if clinically indicated • If no recurrence of grade 3 or higher toxicity after 7 days of nazartinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 or higher toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 2, then resume at ↓ 1 dose level of nazartinib. • If no recurrence of grade 3 or higher toxicity after 7 days of nazartinib monotherapy at ↓ 1 dose level, resume capmatinib at ↓ 1 dose level
RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose levels of nazartinib and capmatinib
Grade 2 (> 1.5 and ≤ 3.0 x baseline; or > 1.5 and ≤ 3 × ULN)	Omit study treatment until resolved to ≤ grade 1 or baseline, then resume treatment at the same dose level of nazartinib and capmatinib
Grade 3 (> 3.0 x baseline; or > 3.0 and ≤ 6.0 × ULN)	Omit study treatment until resolved to ≤ grade 1, then resume nazartinib at the same dose level:

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	• If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 toxicity on maintained dose of nazartinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 1, then resume nazartinib at same dose level and Capmatinib ↓ 1 dose level • If recurrence of grade 3 toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 1 or baseline, then resume nazartinib ↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy at ↓ 1 dose level, resume capmatinib at ↓ 1 dose level
Grade 4 (> 6.0 × ULN)	Discontinue capmatinib permanently and omit nazartinib until resolved to ≤ grade 1 or baseline, then resume nazartinib at same dose level.
HEPATIC[b]	
Isolated Total Bilirubin elevation (for participants with Gilbert Syndrome these dose modifications apply to changes in direct [conjugated] bilirubin only)	
Grade 1 (> ULN – 1.5 x ULN)	Maintain nazartinib and capmatinib dose level
Grade 2 (> 1.5 and ≤ 3.0 × ULN)	Omit study treatmentMonitor LFTs[c] weekly, or more frequently if clinically indicated until resolved to ≤ grade 1, then resume nazartinib and capmatinib at the same dose level.
Grade 3 (> 3.0 and ≤10.0 × ULN)[g]	Omit study treatment. Monitor LFTs[c] weekly, or more frequently if clinically indicated until resolved to ≤ grade 1, then resume nazartinib at the same dose level. • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 toxicity on maintained dose level of nazartinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 1, then resume nazartinib at same dose level and Capmatinib ↓ 1 dose level • If recurrence of grade 3 toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume nazartinib at ↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy at ↓ 1 dose level, resume capmatinib at ↓ 1 dose level
Grade 4 (> 10.0 × ULN)[g]	Discontinue participant permanently from capmatinib and nazartinib. The participant should be monitored weekly (including LFTs[c]), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT elevation	
Grade 2 (> 3.0 and ≤5.0 × ULN)	Maintain dose level of both drugs with LFTs[c] monitored per protocol. Repeat LFTs[c] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[c] weekly, or more frequently if clinically indicated, until resolved to ≤ grade 1.
Grade 3 (> 5.0 - 20.0 × ULN)	Omit study treatment. Monitor LFTs[c] weekly, or more frequently if clinically indicated until resolved to ≤ grade 1, then resume nazartinib at the same dose level: ● If resolved in ≤ 7 days, then resume capmatinib at same dose level ● If resolved in > 7 days, then resume capmatinib at ↓ 1 dose level ● If recurrence during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume nazartinib at ↓ 1 dose level ● If no recurrence after 7 days of nazartinib monotherapy at ↓ 1 dose level, then resume capmatinib at ↓ 1 dose level
Grade 4 (> 20.0 x ULN)	Mandatory: Permanently discontinue both study drugs.

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	Repeat LFTs[c] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[c] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
Combined[d] elevations of AST or ALT and concurrent Total bilirubin[f]	
For participants with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 × ULN combined with total bilirubin > 2.0 × ULN without evidence of cholestasis[e] or For participants with elevated baseline AST or ALT or total bilirubin value: [AST or ALT> 3x baseline or [AST or ALT > 8.0 × ULN], whichever is lower, combined with [total bilirubin >2x baseline AND >2.0 × ULN]	Permanently discontinue nazartinib and capmatinib in the absence of signs of cholestasis, hemolysis, and if alternative causes of the liver injury have been excluded (e.g., concomitant use of hepatotoxic drug(s), alcoholic hepatitis, viral hepatitis etc.) Repeat LFTs[c] as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilized over 4 weeks.
METABOLIC[h]	
Amylase and/or lipase elevation	
Grade 3 (>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic)	Omit study treatment until resolved to ≤ grade 1, then resume nazartinib at the same dose level: • If resolved in ≤ 14 days, resume capmatinib at the same dose level • If resolved in > 14 days, resume capmatinib at↓ 1 dose level • If recurrence of grade 3 toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 2, then ↓ 1 dose level nazartinib • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy at ↓ 1 dose level, resume capmatinib at ↓ 1 dose level
Grade 4 (>5.0 x ULN and with signs or symptoms)	Permanently discontinue capmatinib and omit nazartinib until resolved to grade ≤ 2, then maintain dose level of nazartinib. Monitor for recurrence of grade 3 toxicity after 7 days or sooner if clinically indicated
Note: Perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology. Withhold study treatment for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; if diagnosed with pancreatitis ≥ grade 3 permanently discontinue from capmatinib treatment.	
HBV and HCV reactivation Refer to Table 6-10, Table 6-11 and Table 6-12, and Section 6.3.2 for details.	
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs)	Omit study treatment until resolved to ≤ grade 1then: • If resolved in ≤ 7 days, resume capmatinib at same dose level and nazartinib at ↓ 1 dose level • If resolved in > 7 days, resume capmatinib and nazartinib at ↓ 1 dose level
Grade 4 ([QT/QTc ≥ 501 or > 60 ms change	Permanently discontinue nazartinib and capmatinib.

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia])	Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.
VASCULAR DISORDERS	
Hypertension CTCAE grade 3 for at least 7 days, despite treatment	Omit nazartinib dose until resolved ≤ grade 1, then maintain dose level of capmatinib and re-evaluate after 7 days, or sooner if clinically indicated • If no recurrence of grade 3 toxicity after 7 days of capmatinib monotherapy, resume nazartinib at ↓ 1 dose level • If recurrence of grade 3 toxicity during capmatinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume capmatinib ↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of capmatinib monotherapy at ↓ 1 dose level, resume nazartinib at ↓ 1 dose level
CTCAE grade 4	Discontinue capmatinib and nazartinib
GASTROINTESTINAL	
Diarrhea[e]	
Grade 1	Maintain dose levels of both study drugs but institute anti-diarrheal treatment
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then maintain dose levels of both study drugs.
Grade ≥3 (despite maximal anti-diarrheal medication)	Omit study treatment until resolved to ≤ grade 1, then resume capmatinib at same dose level • If no recurrence of grade 3 toxicity after 7 days of capmatinib monotherapy, resume nazartinib at ↓ 1 dose level • If recurrence of grade 3 toxicity during capmatinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume capmatinib ↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of capmatinib monotherapy at ↓ 1 dose level, resume nazartinib at same dose level
Dose modifications apply to participants who experience diarrhea despite appropriate anti-diarrheal medication. This medication should be started at the first sign of diarrhea.	
Nausea	
Grade 1 or 2	Maintain dose levels of both study drugs but adjust anti-emetic treatment
Grade ≥3 (despite standard anti-emetics)	Omit study treatment until resolved to ≤ grade 1, then resume nazartinib at samedose level • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 1, then ↓ 1 dose level capmatinib • If no recurrence of grade 3 toxicity after 7 days of capmatinib monotherapy at ↓ 1 dose level, resume nazartinib at same dose level
Vomiting	
Grade 1	Maintain dose levels of both study drugs but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Omit study treatment until resolved to ≤ grade 1, then maintain dose levels of both drugs.
Grade ≥3 (despite standard anti-emetics)	Omit study treatment until resolved to ≤ grade 1, then resume nazartinib at same dose level

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	• If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 1, then ↓ 1 dose level capmatinib • If no recurrence of grade 3 toxicity after 7 days of capmatinib monotherapy at ↓ 1 dose level, resume nazartinib at same dose level
Grade 4 (despite standard anti-emetics)	Discontinue study treatment
Dose modifications apply to participants who experience nausea and/or vomiting despite appropriate antiemetic medication. This medication should be started at the first sign of nausea and/or vomiting.	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Stevens-Johnson Syndrome (SJS) or Lyell syndrome/Toxic Epidermal Necrolysis (TEN)	Permanently discontinue study treatment and manage per institutional guidelines.
Rash[j]	
Grade 1 Macules/papules covering <10% BSA (Body Surface Area)	Maintain dose levels of nazartinib and capmatinib
Grade 2 Macules/papules covering 10 - 30% BSA	Maintain dose levels of nazartinib and capmatinib
Grade 3 Macules/papules covering >30% BSA	Omit study treatment until resolved to ≤grade 1, then resume capmatinib at the same dose level. • If no recurrence of grade 3 toxicity after 7 days of capmatinib monotherapy, resume nazartinib at ↓ 1 dose level • If recurrence of grade 3 toxicity during capmatinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume capmatinib↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of capmatinib monotherapy at ↓ 1 dose level, resume nazartinib at same dose level
Grade 4	Permanently discontinue study treatment
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Pneumonitis/Interstitial lung disease	
Grade 1	Interrupt study treatment 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 and nazartinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib and nazartinib may be resumed at the same dose. If it recurs after resumption of study drug, permanently discontinue capmatinib and nazartinib.
Grade 2	Mandatory: Omit capmatinib and nazartinib during diagnostic workup for ILD/pneumonitis 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 and nazartinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib and nazartinib may be resumed following these guidelines: • If resolves to ≤ Grade 1 in ≤ 7 days capmatinib and nazartinib at ↓1 dose level

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	• If fails to resolve to ≤ Grade 1 within 7 days or recurs after resumption of capmatinib and nazartinib at ↓1 dose level , permanently discontinue capmatinib and nazartinib.
Grade 3 OR Grade 4	Permanently discontinue study treatment.
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue/ Asthenia	
Grade 1 or 2	Maintain dose levels of nazartinib and capmatinib
Grade 3	Omit study treatment until resolved to ≤ grade 1, then resume nazartinib at the same dose level: • If resolved in ≤ 7 days, then resume capmatinib at same dose level • If resolved in > 7 days, then resume capmatinib ↓ 1 dose level • If recurrence of grade 3 toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume nazartinib at ↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy at ↓ 1 dose level, resume capmatinib at same dose level
Peripheral edema	
Grade 1 or 2	Maintain dose levels of nazartinib and capmatinib
Grade 3	Omit study treatment until resolved to ≤ grade 1, then resume nazartinib at same dose level and re-evaluate after 7 days, or sooner if clinically indicated • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 toxicity on maintained dose of nazartinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 1, then resume capmatinib at↓ 1 dose level and maintain dose level of nazartinib • If recurrence of grade 3 toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume nazartinib at↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy at ↓ 1 dose level, resume capmatinib at ↓ 1 dose level
Grade 4	Permanently discontinue capmatinib and omit dose of nazartinib until resolved to ≤ grade 1, then continue nazartinib monotherapy
Eye Disorders (Results and images of ophthalmic examinations should be made available upon request)	
Grade 1 or 2 Uveitis/Retinopathy	Maintain dose level of both study drugs, and refer to an ophthalmologist for ophthalmic monitoring at least every 14 days.
Grade 3 Uveitis/Retinopathy	Omit study treatment until resolved to ≤ grade 1, and refer to an ophthalmologist for ophthalmic monitoring at least once a week, then: • If resolved in ≤ 14 days, then resume capmatinib at same dose level and nazartinib at↓ 1 dose level • If resolved in > 14 days, then permanently discontinue participant from nazartinib and resume capmatinib at same dose level
Grade 4 Uveitis/Retinopathy	Permanently discontinue nazartinib and refer the participant to an ophthalmologist for monitoring. Resumption of nazartinib following resolution to ≤ grade 1 may be considered if approved by ophthalmologist and after documented discussion with Novartis. Resume capmatinib at same dose level upon resolution to ≤ grade 1.
Retinal vein occlusion of any Grade	Permanently discontinue nazartinib and refer the participant to an ophthalmologist immediately for monitoring. Resumption of nazartinib following resolution to ≤ grade

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	1 may be considered may be considered if approved by ophthalmologist and after documented discussion with Novartis. Resume capmatinib at same dose level upon resolution to ≤ grade 1.
Other ocular/visual toxicity	
Grade 1 or 2	Maintain dose levels of both drugs, and within one week refer to an ophthalmologist for ophthalmic monitoring at least every 14 days.
Grade 3	Omit study treatments until resolved to ≤ grade 1, and within one week refer to an ophthalmologist for ophthalmic monitoring at least once a week, then: • If resolved in ≤ 14 days, then resume capmatinib at same dose level and nazartinib at↓ 1 dose level • If resolved in > 14 days, then discontinue participant from nazartinib and resume capmatinib ↓ 1 dose level
Grade 4	Permanently discontinue nazartinib, omit capmatinib and refer the participant to an ophthalmologist immediately for monitoring. Resumption of nazartinib at ↓ 1 dose level following resolution to ≤ grade 1 may be considered if approved by ophthalmologist and after documented discussion with Novartis. Resume capmatinib at same dose level upon resolution to ≤ grade 1.
Other adverse events	
Grade 1 or 2	Maintain dose levels of nazartinib and capmatinib
Grade ≥3	Omit study treatment until resolved to ≤ grade 1, then resume nazartinib at same dose level of and re-evaluate after 7 days, or sooner if clinically indicated • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 toxicity on maintained dose level of nazartinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 1, then resume nazartinib at↓ 1 dose level and maintain dose level of capmatinib (i.e., both study drugs ↓ 1 dose level from levels at initial occurrence of grade 3 AE) • If recurrence of grade 3 toxicity during nazartinib monotherapy, omit study treatment until resolved to ≤ grade 1, then nazartinib at↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of nazartinib monotherapy at ↓ 1 dose level, resume capmatinib at ↓ 1 dose level

All dose modifications should be based on the worst preceding toxicity.

[a] Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

[b] If grade 3 or 4 hyper-bilirubinemia 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.

[c] LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 × ULN), alkaline phosphatase (fractionated if alkaline phosphatase > 2.0 × ULN) and gamma-glutamyl transpeptidase (GGT). For isolated elevations of any grade of alkaline phosphatase and/or GGT, maintain dose level.

[d] "Combined" defined as: total bilirubin increases to the defined threshold concurrently with ALT/AST increase to the defined threshold

[e] "Cholestasis" defined as: ALP elevation (> 2 × ULN and R value< 2) in participants without bone metastasis, or elevation of ALP liver fraction in participants with bone metastasis Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury

[f] 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

Worst toxicity CTCAE[a] Grade (value)	Recommendation

[g] Note: If total bilirubin > 3.0 × 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.

[h] A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ grade 3 of amylase and/or lipase. If asymptomatic grade 2 elevations of lipase and/or amylase occur again at the reduced dose, participants will be discontinued permanently from study treatment.

[i] Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.

[j] 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).

Table 6-8 Dose modifications for capmatinib monotherapy (or if nazartinib permanently discontinued and capmatinib continued as monotherapy)

Worst toxicity CTCAE Grade[a] during a cycle of therapy	Recommendation
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 fully resolved in ≤ 7 days, resume treatment at the same dose level • If fully resolved in > 7 days, then resume at↓ 1 dose level
Grade 4 (ANC < 500/mm^3; < 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2 and then resume at ↓ 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 fully resolved in ≤ 7 days, then resume at same dose level • If resolved in > 7 days, then resume at ↓ 1 dose level
Grade 4 (PLT < 25,000/mm^3; < 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then resume at ↓ 1 dose level
Febrile Neutropenia	
ANC <1000/mm3 and a single temperature of >38.3°C (101°F) or a sustained temperature of >=38°C (100.4°F) for more than one hour	Omit dose, then: • If resolved in ≤ 7 days, resume treatment at resume at ↓ 1 dose level • If resolved in > 7 days, permanently discontinue 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

Worst toxicity CTCAE Grade[a] during a cycle of therapy	**Recommendation**
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 fully resolved in ≤ 7 days, resume at the same dose level • If fully resolved in > 7 days, then resume at↓ 1 dose level
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Omit dose until resolved to ≤ grade 2 and then resume at↓ 1 dose level If grade 4 toxicity recurs, permanently discontinue 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 at the same dose level.
Grade 3 (> 3.0 - 6.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume at ↓ 1 dose level.
Grade 4 (> 6.0 x ULN)	Permanently discontinue 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 fully resolved in ≤ 7 days, resume at same dose level. • If resolved in > 7 days, resume at↓1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose until resolved to ≤ grade 1, then • If fully resolved in ≤ 7 days, resume at↓ 1 dose level • If fully resolved in > 7 days, permanently discontinue capmatinib treatment
Grade 4 (> 10.0 x ULN)	Mandatory: Permanently discontinue capmatinib treatment
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3 x ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 if grade 2 elevation at baseline) then • If fully resolved in ≤ 7 days, then resume at the same dose level • If fully resolved in > 7 days, resume at ↓ 1 dose level
Grade 4 (> 20.0 x ULN)	Mandatory: Permanently discontinue capmatinib treatment
Combined elevations of AST or ALT and Total Bilirubin [b,c,d]	
For participants with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis or hemolysis OR For participants with elevated baseline AST or ALT or total bilirubin value:	Mandatory: Permanently discontinue capmatinib treatment

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

Worst toxicity CTCAE Grade[a] during a cycle of therapy	**Recommendation**
Grade 4 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then resume at ↓ 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 resume at ↓ 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 fully resolved in ≤ 7 days, then resume at ↓ 1 dose level • If fully resolved in > 7 days (despite appropriate skin toxicity therapy), then permanently discontinue capmatinib treatment
Grade 4, despite skin toxicity therapy	Omit dose and permanently discontinue 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 resumed at the same dose. If it recurs after resumption of capmatinib, permanently discontinue capmatinib.
Grade 2	Mandatory: Interrupt capmatinib dose during diagnostic workup for ILD until improvement to ≤ Grade 1. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib may be resumedfollowing these guidelines: • If resolves to ≤ Grade 1 in ≤ 7 days reduce study drug by 1 dose level • If fails to resolve to ≤ Grade 1 within 7 days or recur after resumption of capmatinib at decreased dose, permanently discontinue capmatinib
Grade 3 and Grade 4	Mandatory: Permanently discontinue capmatinib. Treat with i.v. steroids as clinically indicated. Oxygen therapy as indicated

Worst toxicity CTCAE Grade[a] during a cycle of therapy	**Recommendation**
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 fully resolved in ≤ 7 days, resume at same dose level • If fully resolved in > 7 days, resume at ↓ 1 dose level
Grade 4	Permanently discontinue capmatinib
Peripheral edema	
Grade 1 or 2	Maintain dose level.
Grade 3	Omit dose until resolved to ≤ Grade 1, then resume at↓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 activities of daily living), consider omitting the dose until resolved to ≤ grade 1, then resume either at same dose or ↓ 1 dose level.
Grade 3	Omit dose until resolved to ≤ grade 1, then resume at↓ 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 metastasis, or elevation of ALP liver fraction in participants with bone metastasis

[d] If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction

* Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the 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)

Table 6-9 Dose modifications for nazartinib (if capmatinib permanently discontinued and nazartinib continued as monotherapy)

Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	Recommendations
HEMATOLOGICAL	
Neutrophil count decreased (ANC) Neutropenia	
Grade 1 (ANC <LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC <1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC <1000 - 500/mm^3)	Omit dose until resolved ≤ Grade 2, then maintain dose level
Grade 4 (ANC <500/mm^3)	Recommendation: omit dose until resolved to ≤ Grade 2, then resume at↓ 1 dose level
Febrile Neutropenia	
(ANC <1.0 x 10^9/L, fever ≥ 38.5°C)	Recommendation: omit dose until resolved, then resume at ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT <LLN - 75,000/mm^3)	May maintain dose level
Grade 2 (PLT <75,000 - 50,000/mm^3)	May maintain dose level
Grade 3 (PLT <50,000 - 25,000/mm^3)	• Recommendation: omit dose until resolved to ≤ Grade 1, then: • If fully resolved in ≤ 7 days, then resume at same dose level • If fully resolved in >7 days, then resume at ↓ 1 dose level
Grade 4 (PLT <25,000/mm^3)	Recommendation: omit dose until resolved to ≤ Grade 1, then resume at ↓ 1 dose level
RENAL	
Serum creatinine	
Grade 1 (>ULN - 1.5 x ULN)-	May maintain dose level
Grade 2 (>1.5 – 3,.0 x ULN)	Recommendation: omit dose until resolved to ≤ Grade 1 or baseline, then resume at same dose level
Grade 3 (>3.0 – 6.0 x ULN	Recommendation: omit dose and discontinue nazartinib
Grade 4 (>6.0 x ULN)	Recommendation: omit dose and discontinue nazartinib
HEPATIC[b]	
Isolated Total Bilirubin (for participant s with Gilbert Syndrome these dose modifications apply to changes in direct [conjugated] bilirubin only)	
Grade 1 (>ULN -1.5 x ULN)	Recommendation: maintain dose level
Grade 2 (>1.5 - 3.0 x ULN)	Recommendation: omit dose. Monitor LFTs[c] weekly, or more frequently if clinically indicated until resolved to ≤ 1.5 x ULN, then: • If fully resolved in ≤14 days, then resume at same dose level • If fully resolved in >14 days, then resume at↓1 dose level
Grade 3 (>3.0 - 10.0 x ULN[g])	Recommendation: omit dose. Monitor LFTs[c] weekly, or more frequently if clinically indicated until resolved to ≤ 1.5 x ULN, then: • If fully resolved in ≤14 days, then resume at↓1 dose level

Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	**Recommendations**
	• If fully resolved in □14 days, then discontinue nazartinib. The participant should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilization over 4 weeks.
Grade 4 (>10.0 x ULN[g])	Mandatory: Permanently discontinue nazartinib The participant should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilized over 4 weeks.
Isolated AST or ALT	
Grade 1: >ULN - 3.0 x ULN	Recommendation: maintain dose level
Grade 2: >3.0 - 5.0 x ULN AND For participants with baseline value ≤ 3.0 x ULN	Recommendation: maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48- 72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
Grade 2: >3.0 - 5.0 x ULN AND For participants with baseline value > 3.0 -5.0 x ULN	Maintain dose level
Grade 3: >5.0 - 10.0 x ULN AND For participants with baseline value ≤ 3.0 x ULN	Recommendation: omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN Then • If fully resolved in ≤ 14 days, resume at same dose level • If resolved in > 14 days, resume at↓ 1 dose level
Grade 3: >5.0 - 10.0 x ULN AND For participants with baseline value > 3.0 -5.0 x ULN	Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b], weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN
Grade 3: >5.0 - 10.0 x ULN AND If AST or ALT > 5 x ULN in participants with baseline AST or ALT ≤ 3 x ULN, or if AST or ALT > 8 x ULN in participants with baseline AST or ALT > 3 x ULN but ≤ 5 x ULN	Mandatory: Immediate testing for viral hepatitis infection or reactivation should be performed, see Section 6.3.2. Participants who have HBV-DNA or HCV-RNA monitoring during the study should be re-tested immediately
Grade 3: >5.0 - 10.0 x ULN AND > 10.0 - 20.0 x ULN	Mandatory: Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ Grade 1 (or to baseline), then resume at↓ 1 dose level.
Grade 4: > 20.0 x ULN	
For participants deriving clinical benefit upon investigator's judgement	Mandatory: Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3 x ULN (or ≤ 5 x ULN for participants with baseline value > 3.0 -5.0 x ULN),

Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	**Recommendations**
	then resume at ↓ 1 dose level. Only 1 dose reduction is allowed; if reoccurs at > 5 x ULN, discontinue nazartinib
For all other participants:	Mandatory: Permanently discontinue participant from study drug treatment Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
Combined[d] elevation of AST or ALT and concurrent Total bilirubin[f]	
For participants with normal baseline ALT, AST and total bilirubin value: AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[e] OR For participants with elevated baseline AST or ALT or total bilirubin value: [AST or ALT>2x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin >2x baseline AND >2.0 x ULN]	Mandatory: Permanently discontinue nazartinib. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks.
METABOLIC[h]	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (>ULN - 1.5 x ULN)	May maintain dose level
Grade 2 (>1.5 - 2.0 x ULN)	May maintain dose level
Grade 3 (>2.0 - 5.0 x ULN)	Recommendation: omit dose until resolved to Grade ≤ 2, then: If fully resolved in ≤ 14 days, then resume at same dose level If fully resolved in >14 days, then resume at↓ 1 dose level
Grade 4 (>5.0 x ULN)	Recommendation: Omit dose and discontinue nazartinib
Note: withhold nazartinib for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
HBV and HCV reactivation Refer to Table 6-10, Table 6-11 and Table 6-12, and Section 6.3.2 for details.	
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTc 450-480 ms)	May maintain dose level
Grade 2 (QTc 481-500 ms)	May maintain dose level
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs)	Recommendation: omit dose until QTc is less than 481 ms and then resume at↓ 1 dose level • Perform an analysis of serum potassium, and if below lower limit of normal, correct with supplements to within normal limits. Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTc <481 ms

Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	**Recommendations**
	• Repeat ECGs 7 days after dose resumption for all participants who had therapy interrupted due to QTc ≥ 501 ms.
Grade 4 (QTcF ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Recommendation: discontinue nazartinib
Bradycardia	
Grade 1 or 2	Recommendation: omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm Evaluate concomitant medications known to cause bradycardia and adjust the dose of nazartinib
Grade 3	Recommendation: omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm
Grade 4 (in participants taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	If the concomitant medication can be adjusted or discontinued, resume nazartinib at ↓ 1 dose level with frequent monitoring
Grade 4 (in participants who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension)	Recommendation: permanently discontinue nazartinib
Vascular disorders	
Hypertension	
Grade 3	Recommendation: omit dose until resolved ≤ Grade 1, then resume at↓ 1 dose level
Grade 4	Recommendation: omit dose and discontinue nazartinib
GASTROINTESTINAL	
Diarrhea[i]	
Grade 1 (despite maximal anti-diarrheal medication)	Recommendation: maintain dose level but adjust anti-diarrhea treatment
Grade 2 (despite maximal anti-diarrheal medication)	Recommendation: omit dose until resolved to ≤ Grade 1, then resume at same dose level. If diarrhea returns as ≥ Grade 2, then omit dose until resolved to ≤ Grade 1, then resume at↓ 1 dose level
Grade 3 (despite maximal anti-diarrheal medication)	Recommendation: omit dose until resolved to ≤ Grade 1, then resume at ↓ 1 dose level
Grade 4 (despite maximal anti-diarrheal medication)	Recommendation: omit dose until resolved to ≤ Grade 1, then resume at↓ 1 dose level
Nausea	
Grade 1 or 2	Recommendation: maintain dose level but adjust anti-emetic treatment
Grade 3 (despite standard anti-emetics)	Recommendation: omit dose until resolved to ≤ Grade 1, then resume at↓ 1 dose level
Vomiting	
Grade 1 (despite standard anti-emetics)	Recommendation: maintain dose level but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Recommendation: omit dose until resolved to ≤ Grade 1, then resume at same dose level.

Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	**Recommendations**
	If vomiting returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then resume at↓ 1 dose level
Grade 3 (despite standard anti-emetics)	Recommendation: omit dose until resolved to ≤ Grade 1, then resume at↓ 1 dose level
Grade 4 (despite standard anti-emetics)	Recommendation: omit dose until resolved to ≤ Grade 1, then resume at↓ 1 dose level
Dose modifications apply to participants who experience nausea and/or vomiting despite appropriate antiemetic medication. This medication should be started at the first sign of nausea and/or vomiting.	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Rash/photosensitivity Refer to Table 6-13, Table 6-14 , and Table 6-15 for management and dose modification for rash/skin toxicities	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Pneumonitis/Interstitial lung disease Refer to Table 6-16 for management and dose modification for non-infectious pneumonitis/interstitial lung disease	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue/ Asthenia	
Grade 1 or 2	May maintain dose level
Grade 3	Recommendation: omit dose until resolved to ≤ grade 1, then: If fully resolved in ≤ 7 days, then reseum at same dose level If fully resolved in > 7 days, then resume at↓ 1 dose level
Metabolic	
Any Grade **hypophosphatemia**	Treatment with phosphate supplements as clinically indicated and maintain dose level
Persistent **hyperglycemia** (glucose > 250 mg/dL) despite optimal anti-hyperglycemic therapy	Omit dose until hyperglycemia is adequately controlled then resume nazartinib at ↓ 1 dose level If adequate hyperglycemic control cannot be achieved with optimal medical management permanently discontinue nazartinib
Other adverse events	
Grade 1 or 2	May maintain dose level
Grade 3	Recommendation: omit dose until resolved to ≤ grade 1, then resume at↓ 1 dose level
Grade 4	Recommendation: omit dose and then discontinue nazartinib. Note: Omit dose for ≥ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)
All dose modifications should be based on the worst preceding toxicity. [a] Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [b] If Grade 3 or 4 hyper-bilirubinemia 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. [c] LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin >2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase > 2.0 x ULN) and gamma-glutamyl transpeptidase (GGT). For isolated elevations of any grade of alkaline phosphatase and/or GGT, maintain dose level. [d] "Combined" defined as: total bilirubin increases to the defined threshold concurrently with ALT/AST increase to the defined threshold	

Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	Recommendations
[e] "Cholestasis" defined as: ALP elevation (>2xULN and R value< 2) in participants without bone metastasis, or elevation of ALP liver fraction in participants with bone metastasis Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury [f] 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 [g] 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. [h] A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, participants will be discontinued permanently from study treatment. [i]Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.	

6.3.2 Guidelines for screening, monitoring and management of HBV / HCV reactivation

HBV screening tests, on study monitoring, and management of HBV reactivation

1. All participants must be screened with HBV serologic markers: HBsAg, HBsAb, and HBcAb.
2. If HBsAg and/or HBcAb are positive, test for HBV-DNA.
3. Refer to Table 6-10 for actions to be taken based on screening HBV results.
4. If a participant is HBsAg positive or HBV-DNA positive BUT is not on antiviral therapy:
   a. Consult a physician with expertise in managing HBV
   b. Initiate antiviral therapy with entecavir 0.5 mg q.d. 1-2 weeks prior to first dose of study treatment (capmatinib + nazartinib). Note: ongoing participants prior to initiation of Amendment 3 follow the Urgent Safety Measure.
   c. If a participant cannot take entecavir or if entecavir is not available at your institution, contact Novartis to select an appropriate antiviral therapy.
   d. If antiviral therapy cannot be given, the participant is not eligible for study treatment (capmatinib +nazartinib).
   e. During the study, monitor HBV-DNA every 4 weeks (or more frequently if clinically indicated). (Refer to Table 6-11 if there is evidence of viral reactivation on study)
   f. Antiviral therapy should continue for at least 4 weeks after the last dose of study treatment (capmatinib + nazartinib).
5. Participants who are HBsAg positive or HBV-DNA positive at screening and already have been receiving antiviral therapy are eligible provided the participant remains on antiviral treatment.
   a. Identify a consulting physician with expertise in managing HBV who can provide treatment guidance, if required, while the participant is on study.
   b. HBV-DNA should be monitored every 4 weeks (or more frequently if clinically indicated).
   c. Antiviral therapy should continue for at least 4 weeks after the last dose of study treatment (capmatinib +nazartinib).
6. Refer to Table 6-11 for guidelines of management for HBV reactivation.

Table 6-10 Actions to be taken based on hepatitis B results screening

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+ and no prior HBV vaccination	- or + with prior HBV vaccination	- or + with prior HBV vaccination
HBcAb	+ or -	+ or -	+ or -	+	-
Required actions	* Consult a physician with expertise in managing HBV. After the consultation, antiviral therapy should be started 1-2 weeks prior to first dose of study treatment (capmatinib + nazartinib). Recommended antiviral therapy is entecavir 0.5 mg q.d. Contact Novartis if a participant cannot take entecavir or if entecavir is not available at your institution. Monitor HBV-DNA every 4 weeks (or more frequently if clinically indicated). Antiviral therapy should continue for at least 4 weeks after the last dose of study treatment (capmatinib + nazartinib).		No antiviral therapy. Monitor HBV-DNA every 4 weeks.		No antiviral therapy. HBV-DNA screening not required unless if HBsAg and/or HBcAb are positive
*Recommended antiviral therapy is entecavir 0.5 mg q.d. Contact Novartis if a participant cannot take entecavir or if entecavir is not available at your institution. Antiviral therapy should continue for at least 4 weeks after the last dose of study treatment (capmatinib + nazartinib).					

Table 6-11 Guidelines for management of HBV reactivation

HBV reactivation (with or without clinical signs and symptoms)*		
Screening test results	**Monitoring test results that define HBV reactivation**	**Actions to be taken**
Positive HBV-DNA OR Positive HBsAg	Increase of 1 log in HBV-DNA relative to screening HBV-DNA value OR new appearance of measurable HBV-DNA	Interrupt study treatment (capmatinib + nazartinib). Assess participant compliance with antiviral therapy. Consult a physician with expertise in managing HBV and consider changing antiviral therapy. While participant is on antiviral therapy, continue interruption of study treatment (capmatinib + nazartinib) administration until resolution to: • ≤ screening HBV-DNA levels **and** • ≤ grade 1 ALT (or baseline ALT, if > grade 1) if ALT elevation was observed **If resolution occurs within ≤ 21 days** study treatment (capmatinib + nazartinib) should be re-started at the same dose level unless dose reduction/interruption is indicated due to any other reason. Antiviral therapy should continue for at least 4 weeks after the last dose of study treatment (capmatinib + nazartinib). If resolution occurs > 21 days Contact Novartis for approval of restarting of study treatment (capmatinib + nazartinib). • If restarting of study treatment (capmatinib + nazartinib) is approved: follow the same guidelines as above.

HBV reactivation (with or without clinical signs and symptoms)*		
Screening test results	**Monitoring test results that define HBV reactivation**	**Actions to be taken**
		• If restarting of study treatment (capmatinib + nazartinib) is NOT approved: discontinue study treatment (capmatinib + nazartinib). Continue antiviral therapy for at least 4 weeks after the last dose of study treatment (capmatinib + nazartinib). Monitor HBV-DNA every 4 weeks (or more frequently if clinically indicated).
Negative HBV-DNA AND Negative HBsAg	New appearance of measurable HBV-DNA	Interrupt study treatment (capmatinib + nazartinib). Consult a physician with expertise in managing HBV. After the consultation, start antiviral therapy. While participant is on antiviral therapy, continue interruption of study treatment (capmatinib + nazartinib) administration until resolution to: • ≤ baseline HBV-DNA levels **and** • ≤ grade 1 ALT (or baseline ALT, if > grade 1) if ALT elevation was observed **If resolution occurs within ≤ 21 days** study treatment (capmatinib + nazartinib) should be re-started at the same dose level unless dose reduction/interruption is indicated due to any other reason. Antiviral therapy should continue for at least 4 weeks after the last dose of study treatment (capmatinib + nazartinib). **If resolution occurs > 21 days** Contact Novartis for approval of restarting of study treatment (capmatinib + nazartinib). • If restarting of study treatment (capmatinib + nazartinib) is approved: follow the same guidelines as above. • If restarting of study treatment (capmatinib + nazartinib) is NOT approved: discontinue study treatment (capmatinib + nazartinib). Continue antiviral therapy for at least 4 weeks after the last dose of study treatment (capmatinib + nazartinib). Monitor HBV-DNA every 4 weeks (or more frequently if clinically indicated).
* All reactivations of HBV are to be recorded as serious adverse event (SAE). Date of viral reactivation is the date on which the defined lab results for reactivation were met (e.g. for a participant who was HBV-DNA positive on 01-JAN-15 and whose ALT reached > 5 × ULN on 01-APR-15, the date of viral reactivation is 01-APR-15).		

HCV screening tests, on study monitoring, and management of HCV reactivation

1. Screen all new participants for HCV Ab. If HCV Ab is detected then check HCV-RNA.
2. Only participants with negative HCV Ab or with positive HCV Ab but undetectable level of HCV-RNA are eligible to be dosed with study treatment (capmatinib + nazartinib) (assuming all other eligibility criteria are met). Participants with detectable HCV-RNA are not eligible to be enrolled in the study.
3. The following two categories of participants should be monitored every 8 weeks (or more frequently if clinically indicated) with HCV RNA-PCR for HCV reactivation:
   a. Participants with detectable HCV-RNA at screening and were treated until HCV-RNA becomes undetectable (only applicable to participants enrolled prior to Amendment 3)
   b. Participants with known history of HCV infection and undetectable HCV-RNA at screening
4. Refer to Table 6-12 for definition of HCV reactivation and the management guidelines.

Table 6-12 Guidelines for management of HCV reactivation

HCV reactivation (with or without clinical signs and symptoms)[1]		
Screening test results	**Monitoring test results that define HCV reactivation**	**Action to be taken**
Knowledge of past hepatitis C infection with no detectable HCV-RNA OR Detectable HCV-RNA at screening and was treated until HCV-RNA becomes undetectable[2]	New appearance of detectable HCV-RNA	Interrupt study treatment (capmatinib + nazartinib). Consult a physician with expertise in managing HCV. After the consultation, start antiviral therapy. While participant on antiviral therapy, continue interruption of study treatment (capmatinib + nazartinib) administration until resolution to: • no detectable HCV-RNA **and** • ≤ grade 1 ALT (or baseline ALT, if > grade 1) if ALT elevation was observed. **If resolution occurs within ≤ 21 days** study treatment (capmatinib + nazartinib) should be re-started at the same dose level unless dose reduction/interruption is indicated due to any other reason. **If resolution occurs > 21 days** Contact Novartis for approval of restarting of study treatment (capmatinib + nazartinib). • If restarting of study treatment (capmatinib + nazartinib) is approved: follow the same guidelines as above. • If restarting of study treatment (capmatinib + nazartinib) is NOT approved: permanently discontinue the participant from study treatment (capmatinib + nazartinib). Monitor HCV-RNA every 4 weeks (or more frequently if clinically indicated)
[1] All reactivations of HCV are to be recorded as serious adverse event (SAE). Date of viral reactivation is the date on which the defined lab results for reactivation were met (e.g., for a participant whose HCV-RNA was detectable on 01-JAN-15 and ALT reached > 5 x ULN on 22-JAN-15, the date of viral reactivation is 22-JAN-15). [2] Applicable to ongoing participants only		

On study monitoring of liver function test (LFT) for all participants

LFTs should be monitored for all participants as per protocol, or more frequently if clinically indicated.

At any time during the study, if ALT > 5 x ULN in participants with baseline ALT ≤ 3 x ULN, or if ALT > 8 x ULN in participants with baseline ALT > 3 x ULN but ≤ 5 x ULN: **immediately**

1. Perform test(s) for viral hepatitis infection or reactivation: all participants should be screened with viral hepatitis panel (HA Ab-IgM, HBsAg, HBcAb-IgM, and HC Ab). In addition
   a. Participants who have HBV-DNA monitoring during the study should be re-tested for HBV-DNA immediately; refer to Table 6-11 for definition and management of HBV reactivation.
   b. Participants who have HCV-RNA monitoring during the study should be re-tested for HCV-RNA immediately; refer to Table 6-12 for definition and management of HCV reactivation.
2. If any of the above tests indicate:

a. HBV reactivation: refer to Table 6-11 for management guidelines.
b. HCV reactivation: refer to Table 6-12 for management guidelines.
c. New viral infection: immediately interrupt study treatment (capmatinib + nazartinib), consult a physician with expertise in managing viral hepatitis and contact Novartis for further discussion.

3. Perform other relevant tests/procedures as clinically indicated.
4. Follow the dosing modification for ALT elevation according to guidelines in Table 6-7.

6.3.3 Guidelines for the management and dose modification of skin-related toxicities

Rash, particularly maculopapular rash or rash pruritic, is an adverse event frequently observed following treatment with nazartinib. Participants must be closely monitored for any signs/symptoms related to rash/skin toxicities. Recommended guidelines for management and dose modification of rash/skin toxicities are provided in Table 6-13, Table 6-14, and Table 6-15.

Recommended dose modifications apply to both nazartinib and capmatinib.

Table 6-13 Guidelines for prevention and symptomatic care of rash/skin toxicities

Type of care	Action
Prevention/Prophylaxis Starting from Day 1 for all participants	• Avoid unnecessary exposure to sunlight/ultraviolet • Apply broad-spectrum sunscreen with SPF≥15 at least twice daily • Use thick, alcohol-free emollient cream (e.g. glycerine and cetomacrogol cream) on dry areas of the body at least twice daily
Symptomatic care*	• Pruritic lesions: cool compresses and oral antihistamine therapies • Desquamation: thick, alcohol-free emollient cream and mild soap • Paronychia: antiseptic bath and topical antibiotics; if no improvement, consult dermatologist • Infected lesions: appropriate topical or systemic antibiotics
*Participants who develop rash/skin toxicities should be evaluated by a qualified physician and receive symptomatic and supportive care management.	

Table 6-14 Management and dose modification for maculopapular rash[1, 2]

Initial CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• Initiate appropriate symptomatic care (Refer to Table 6-13) • Use mild-strength topical steroid (e.g. 1% hydrocortisone cream) on affected areas • Re-assess every week	Continue nazartinib and capmatinib at same dose level
Grade 2	• Initiate appropriate symptomatic care (Refer to Table 6-13) • Use moderate-strength topical steroid (e.g. 2.5% hydrocortisone cream or 0.5% fluticasone cream) on affected areas PLUS low-dose oral steroid (e.g. 5 mg-10 mg PO q.d. for 1 week) with taper	Continue nazartinib and capmatinib at same dose level • If no recovery or worsened within 1 week, interrupt nazartinib and capmatinib until recover to ≤ Grade 1. Once rash has recovered to ≤ Grade 1, restart nazartinib and capmatinib at one

Initial CTCAE Grade	Adverse Event Management	Action and Dose Modification
	• Re-assess every week	level reduced from the previous dose level[3]
Grade ≥3	• Initiate appropriate symptomatic care (Refer to Table 6-13) • Use moderate-strength topical steroid on affected areas PLUS mid-dose oral steroid (e.g. 20-40 mg PO q.d. for 1 week) with taper over 1-2 weeks or i.v. steroid (e.g. methylprednisolone 20-30 mg i.v. b.i.d. for 3 days) if clinically indicated • Consult dermatologist • Reassess every week	• Interrupt nazartinib and capmatinib until rash recovers to ≤ Grade 1. Once recovers to ≤ Grade 1, restart study drug at one level reduced from the previous dose level[2]. • Oral antihistamine therapies (e.g. levocetirizine 5 mg q.d., desloratadine 5 mg q.d., or fexofenadine 180 mg q.d.) should be given concurrently with study drug for 4 weeks when restarting treatment. • If no recovery to ≤ Grade 2 within 3 weeks, permanently discontinue study drug • Participants who develop more than 1 episode of Grade ≥ 3 rash will be permanently discontinued from study drug

[1] Maculopapular rash includes macular rash, papular rash, and maculopapular rash.

[2] For all grades of maculopapular rash, consider skin biopsy for pathologic evaluation. Study drugs may be resumed although steroids are still ongoing or being tapered.

[3] A maximum of 2 dose reductions is allowed. Participants, who require further dose decrease after 2 dose reductions, should be discontinued from study drug. Escalation **by one level** to previous dose level may be considered if no rash is evident after 4 weeks of uninterrupted study drug at the reduced dose level. Re-escalation can only be done once.

Table 6-15 Management and dose modification for other rashes including acneiform rash

Initial CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• Monitor for change in severity and consider symptomatic and/or topical treatment (Refer to Table 6-13) • Re-assess every 2 week	Continue study drug at same dose level
Grade 2	• Initiate appropriate symptomatic care (Refer to Table 6-13) • Depending on the type of rash, a variety of agents can be used including mild to moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines, and retinoid creams. • Re-assess every 2 week	Continue study drug at same dose level • If no recovery or worsened within 2 weeks, interrupt study drug until rash recovers to ≤ Grade 1 • Once rash recovers to ≤ Grade 1, then restart study drug at one reduced dose level*
Grade ≥3	• Initiate appropriate symptomatic care (Refer to Table 6-13) • Depending on the type of rash, a variety of agents can be used including mild to moderate strength steroid creams, low-dose oral steroids, etopical or systemic antibiotics, topical or systemic antihistamines, and retinoid creams. • Consult dermatologist • Reassess every 2 week	Interrupt study drug until rash recovers to ≤ Grade 1. -Once rash recovers to ≤ Grade 1, restart study drug at one reduced dose level* • If no recovery to ≤ Grade 2 within 3 weeks, permanently discontinue study drug • Participants who develop more than 1 episode of Grade ≥3 rash will be permanently discontinued from study treatment
*A maximum of 2 dose reductions is allowed. Participants, who require further dose decrease after 2 dose reductions, should be discontinued from study drug. Escalation **by one level** to previous dose level may be considered if no rash is evident after 4 weeks of uninterrupted study drug at the reduced dose. Re-escalation can only be done once.		

6.3.4 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. All participants must be followed up for adverse events and serious adverse events for 30 days following the last doses of nazartinib and capmatinib.

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 6-16 Toxicity follow-up evaluation

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

TOXICITY	FOLLOW-UP EVALUATION
	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.
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: Call the study's central ECG review laboratory immediately and request an immediate manual read of the ECG. 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. If the central ECG report shows a QTcF ≥ 501 msec (not previously documented on the site machine), contact the participant and instruct him/her to suspend capmatinib and return for a repeat ECG as soon as possible. The central ECG reader should be called for a manual read of the repeat ECG immediately, and the above guidance followed.
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).

TOXICITY	FOLLOW-UP EVALUATION
	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/h IV) and antibiotics (e.g., fluoroquinolone) should be given
Nausea and Vomiting	The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of nausea and/or vomiting and remedy these causes if possible (e.g., discontinuation of concomitant medication, dietary modification, treatment of comorbidity). Individualized supportive and anti-emetic treatment should be initiated, as appropriate, at the first signs and/or symptoms of these AEs. In participants with vomiting, the participant should be monitored for signs of dehydration and instructed to take preventive measures against dehydration. Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator's best judgment.
SKIN TOXICITY	
Rash and Photosensitivity	
CTCAE grade 1	Consider to initiate 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 ≤ 1
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

TOXICITY	FOLLOW-UP EVALUATION
	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 Bronchoalveolar Lavage (BAL) recommended [c] Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated) [b]
CTCAE Grade 3 and Grade 4	CT scan (high-resolution with lung windows) Clinical evaluation and laboratory work-up for infection Consult pulmonologist Pulmonary function tests[a] - if < normal, repeat every 8 weeks until ≥ normal Bronchoscopy with biopsy and/or BAL if possible[c] Treat with i.v. steroids (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hr)[b] If i.v. steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication
[a] Pulmonary function tests (PFTs) to include: diffusing capacity of the lungs for carbon monoxide corrected for hemoglobin (DLCO); spirometry; resting oxygen saturation. Guideline for significant deterioration in lung function: [a] 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.	

6.3.4.1 Follow up on potential QTcF prolongation

In case of QTcF >500 ms, (or QTcF prolongation >60 ms from baseline)

- Assess the quality of the ECG recording and the QT value and repeat if needed
- Interrupt study treatment (capmatinib + nazartinib)
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment (capmatinib + nazartinib).
- Review concomitant medication use for other causes for QT prolongation, and for drugs with the potential to increase the risk of drug exposure related QT prolongation
- Check study drug dosing schedule and study treatment compliance
- Consider collecting a time-matched PK sample, and record time and date of last study drugs intake.
- Perform a repeat ECG within one hour of the first QTcF of >500 ms.

After confirming ECG reading at site, if QTcF > 500 ms

- Interrupt study treatment (capmatinib + nazartinib)
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed > 500 ms:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify clinical conditions that could potentially prolong the QT
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as clinically indicated, until the QTcF returns to ≤ 480 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 >500 ms.
- After resolution to ≤ 480 ms, consider re-introducing study treatment (capmatinib + nazartinib) at reduced dose, and increase ECG monitoring:
  - If QTcF remains ≤ 500 ms after dose reduction, continue planned ECG monitoring during subsequent study treatment
  - If QTcF recurs > 500 ms after dose reduction, discontinue participant from trial.

6.3.4.2 Follow up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with total bilirubin increase may be indicative of potential DILI, these cases should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

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

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 3 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]

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 as the cause of liver injury.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, Glutamate dehydrogenase (GLDH), prothrombin time (PT)/INR and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
- 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 ≤ 2), hepatocellular (R ≥ 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 6-17 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities. Guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-17 Guidance to rule out other alternative causes of observed LFT abnormalities

Disease	Assesment
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
Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Epstein-Barr Virus (EBV) infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, Mean Corpuscular Volume (MCV), CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

- Obtain PK sample, as close as possible to last dose of study drug, 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", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.5 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events will be as per institutional guidelines.

Refer to preclinical toxicity [redacted] and clinical data found in the [nazartinib and capmatinib Investigator's Brochure].

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the participant are allowed, except when specifically prohibited (see Section 6.4.3).

The participant must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Surgical and Medical Procedures CRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before enrolling 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.

6.4.1.1 Permitted concomitant therapy of capmatinib in combination with nazartinib

Anticoagulation treatment is also allowed if INR has been established within the therapeutic range prior to study entry. PT and PTT ≥ 1.5x ULN are permitted in these cases.

After discussion with Novartis, participants who develop progressive disease limited to the bone or CNS may undergo radiotherapy to the bone or CNS, and surgical resection of CNS metastases, and remain on study. Nazartinib and capmatinib should be held for at least 5 days prior to radiotherapy or surgery. Nazartinib and capmatinib may be resumed > 3 days after completing radiotherapy or surgery if all procedure-related toxicities have resolved to ≤ Grade 1.

The exception to this is palliative bone radiation, which is permitted throughout the study. However, study treatment should be interrupted on the day of radiotherapy.

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

6.4.1.2 Permitted concomitant therapy of capmatinib monotherapy in Phase II Group 5

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

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

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

- Antibiotics
- Medications to prevent or treat nausea, vomiting or diarrhea
- Growth factors (e.g., Granulocyte-Colony-Stimulating Factor (G-CSF), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), erythropoietin, platelets growth factors, etc.) are allowed per the investigator's judgement and per local guidelines
- Oxygen therapy and blood products or transfusions
- Nutritional support or appetite stimulant
- Pain medication

6.4.2 Permitted concomitant therapy requiring caution and/or action

6.4.2.1 Permitted concomitant therapy of capmatinib in combination with nazartinib requiring caution and/or action

[redacted]

Interactions with transporters

[redacted]

[redacted]

The participant and the Investigator should be aware of potential signs of overdose of the concomitant medication. In the event of suspected toxicity, administration of either nazartinib, Capmatinib or concomitant drugs should be discontinued according to Investigator judgment.

Refer to Table 14-14 in Section 14.3 Appendix for permitted medications that require caution when concomitantly used with nazartinib and capmatinib. If a medication listed in Section 14.4 Appendix appears on both the list of prohibited and the list of medications to be used with caution (Table 14-14 and Table 14-16), the medication is prohibited.

[redacted]

[redacted].Refer to Table 14-15 in Section 14.3 Appendix for a list of the permitted concomitant medications requiring caution with capmatinib monotherapy. If a medication listed in Section 14.4 Appendix appears on both the list of prohibited and the list of medications to be used with caution (Table 14-15 and Table 14-17), the medication is prohibited.

6.4.3 Prohibited concomitant therapy

If during the course of the trial prohibited concomitant medication cannot be avoided study treatment must be interrupted until an assessment of the potential safety risk has been performed.

6.4.3.1 Prohibited concomitant therapy with capmatinib and nazartinib

Antineoplastic therapies

Concomitant antineoplastic therapy (including radiotherapy and surgery) or other investigational treatment is prohibited except as described in Section 6.4.1.

[redacted]

Live vaccines

Live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines, COVID-19 vaccines) must not be administered while a participant is dosed with capmatinib + nazartinib and for 30 days after the last dose of study treatment (capmatinib + nazartinib).

Drug with a known risk of QT prolongation

Medications with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe should not be administered while a participant is dosed with capmatinib + nazartinib and for 30 days after the last dose of study treatment (capmatinib + nazartinib). Such medications

should be discontinued within 5 half-lives or 7 days prior (whichever is longer) to starting study drug or replaced by safe alternative medication. A list of drugs with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe is provided in Table 14-16 in Section 14.3 Appendix and available online at qtdrugs.org. Refer to Table 14-16 in Section 14.3 Appendix for a list of prohibited medications. If a participant must use a drug in Table 14-16 in Section 14.3 Appendix, the participant must be discontinued from the study.

6.4.3.2 Prohibited concomitant therapy with capmatinib monotherapy in Phase II Group 5

Live vaccines

Live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines, COVID-19 vaccines) must not be administered while a participant is dosed with capmatinib monotherapy and for 30 days after the last dose of study treatment.

6.4.4 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 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").

6.4.5 Permitted radiotherapy

Localized palliative radiotherapy for pre-existing, painful bone/liver metastases is permitted. 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 appropriate eCRF pages. After documented progression by RECIST 1.1, radiotherapy is allowed following the same dose adjustment guidance in case capmatinib and osimertinib is continued beyond PD.

6.5 Participant numbering, treatment assignment

This is a non-randomized trial and Integrated Response Technology (IRT) will only be used for distribution of study medication in the Phase II part.

6.5.1 Participant numbering

Each participant is identified in the study by a participant Number (Participant No.), that is assigned when the participant is first enrolled for molecular pre-screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. 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 is numbered uniquely across the entire database. Upon signing the molecular pre-screening or screening informed consent form, the participant is assigned to the next sequential participant No. available to the investigator through the EDCinterface.

For Phase II participants, the investigator or designated staff will contact the IRT at the molecular pre-screening visit and at the screening visit to provide the requested identifying information for participant registration into the IRT.

Once assigned, the participant No. must not be reused for any other participant and the participant No. for that individual must not be changed, even if the participant is re-screened. If the participant fails to be assigned to treatment or start treatment for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the participant was not enrolled.

6.5.2 Treatment assignment

The assignment of a participant to a particular cohort will be coordinated by the sponsor during the Phase Ib part of the study.

For the Phase II part, an IRT will be used to track participant enrollment, document key eligibility criteria, allocate participants into 5 different groups based on their characteristics at study entry, and track individual assignment of capmatinib monotherapy or capmatinib in combination with nazartinib drug supplies. The IRT will dispense the selected capmatinib monotherapy or capmatinib in combination withand nazartinib dose to each participant participating in this trial.

For each allocated participant, and prior to dosing, all participants who fulfill all inclusion/exclusion criteria will be assigned to one of the groups of interest during the Phase II part, and information will be collected via IRT:

- Group 1 (first or second generation TKI resistant): EGFRmut$^{L858R/ex19del}$ NSCLC participants developing resistance to EGFR-TKI:
  - sub-group 1a: EGFRmut$^{L858R/ex19del}$ NSCLC with acquired mutation T790M *(T790M+, MET dysregulation-)*.
  - sub-group 1b: EGFRmut$^{L858R/ex19del}$ NSCLC with demonstrated MET dysregulation *(T790M-, MET dysregulation+)*.
    MET dysregulation is defined as either gene copy number ≥ 4 and/or IHC 3+ (defined as ≥50% of cells staining with high intensity)

  - sub-group 1c: EGFRmut$^{L858R/ex19del}$ NSCLC with either evidence of both acquired T790M and MET dysregulation *(T790M+, MET dysregulation+)*
  - sub-group 1d: EGFRmut$^{L858R/ex19del}$ NSCLC with MET dysregulation below the levels for sub-group b *(T790M-, MET dysregulation-)*.
- Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve): EGFR-TKI naïve NSCLC participants with T790M de novo mutation.
- Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic): EGFRmut$^{L858R/ex19del}$ NSCLC participants, treatment naïve.
- Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic: EGFRmut NSCLC who failed (defined as intolerance to treatment or documented disease progression) maximum 2 prior lines of systemic antineoplastic therapy
- Group 5 (EGFRmut, T790M-, MET GCN≥5, 2L, EGFR TKI resistant): previously documented EGFR activating mutation (e.g., L858R and/or ex19del), T790M negative, MET amplified who have progressed on one prior line of therapy (either to first/second generation EGFR TKIs, osimertinib or other third generation EGFR TKIs) for advanced/metastatic NSCLC disease.

Participants in Phase Ib, Phase II Groups 1, 2 and 3 will take the combination therapy in fasting conditions whilst participants in Phase II Group 4 will take the study treatment with food.

For the purpose of this study, common EGFR activating/sensitizing mutations are L858R point mutation and exon 19 deletions which account for approximately 90% of the cases. Other rare EGFR mutations such as L861Q, G719X, and S768I are also considered activating/sensitizing mutations for enrollment onto the Phase II Group 1, Group 3 and Group 4.

The IRT will also specify medication number of the bottles of capmatinib monotherapy or capmatinib in combination with nazartinib study drug to be dispensed to the participant.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the participant or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the participant by authorized site personnel only. Dose strength and treatment schedule are described in Table 6-1. All dosages prescribed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

As per Section 2.7, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees as appropriate) in the event the investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3 months supply. In this case, regular phone calls or virtual contacts (every 4 weeks (+/- 1 week) or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring

participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

6.6.1 Study drug packaging and labeling

The study medication packaging has a 2-part label.

In Phase Ib responsible site personnel will add the participant number on the label.

In Phase II, a unique medication number will also be printed on each part of this label which corresponds to one of the treatment arms and a specific visit or dose/dose level. Responsible site personnel will identify the study treatment package(s) to dispense to the participant by using the IRT and obtaining the medication number(s). Site personnel will add the participant number on the label.

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

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the participant. Additionally in Phase II, labels will include the unique medication number.

Nazartinib and capmatinib will be supplied by -Novartis Global Clinical Supply. Nazartinib 25 mg, 50 mg and 100 mg capsules, and 25 mg, 50 mg and 200 mg tablets will be packaged in high-density polyethylene (HDPE) bottles. Capmatinib 100 mg, 150 mg and 200 mg tablets will be packaged in HDPE bottles.

For participants in Phase II Group 5, nazartinib and capmatinib will be supplied by Novartis Global Clinical Supply. Nazartinib 25 mg, 50 mg capsules will be packaged in HDPE bottles. Capmatinib 150 mg and 200 mg tablets will be packaged in HDPE bottles.

6.6.2 Drug supply and storage

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

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Participants will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.4 Disposal and destruction

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

Study treatment destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and permitted by local regulations.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 and Table 7-2 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

No CRF will be used as a source document.

Screening/baseline evaluations (including baseline radiological assessments) must be performed ≤ 28 days of Cycle 1 Day 1. Laboratory assessments performed as part of the screening evaluations and within 72 hours of the first dose of study treatment, are not required to be repeated on the first dosing day.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. During the Phase Ib part of the study, for C2D1, a visit window of +3 days is permitted to ensure minimal follow-up of 28 days during cycle 1. For all other visits, a visit window of +/- 3 days is allowed. HBV/HCV results should be available prior to first dose of study treatment (capmatinib + nazartinib). On PK collection days of Cycle 1, the window is only +/- 1 day. PK samples of Cycle 1 Day 1 must be collected at the same day of first dose.

Radiological assessments must be performed +/-7 days of the scheduled date of the assessment.

As per Section 2.7, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local health authority and depending on 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.

Table 7-1 Visit evaluation schedule for Phase Ib and Phase II Groups 1 to 4

			Screening Phase		Treatment Phase														Follow-Up		
	Category	Protocol Section	Pre-Molecular screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		EoT	30-day Safety F/U	Disease progression F/U	Survival F/U every 3 months
Day of Cycle				-28 to 1	1	2	8	15	16	22	1	2	8	15	22	1	15				
Obtain Molecular Pre-screening Informed Consent	D	7.1.1.	X																		
Obtain Main Informed Consent	D	7.1.2.		X																	
IRT Registration (Phase II)		6.5.1.	X	X														X			
Participant history																					
Demography	D	7.1.2.2.	X	X																	
Inclusion/exclusion criteria	D		X	X																	
Current medical conditions	D	7.1.2.2.		X																	
Diagnosis and extent of cancer	D	7.1.2.2.		X																	
Prior antineoplastic therapies	D	7.1.2.2.		X																	
Smoking history	D	7.1.2.2.		X																	
Prior/concomitant medications	D	7.1.2.2.			Continuously														X		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.2.2.																	X	X	X
Physical examination	S	7.2.2.1.		X	X		X	X		X	X		X	X	X	X		X			
Vital signs	D	7.2.2.2.		X	X		X	X		X	X		X	X	X	X		X			
Height	D	7.2.2.3.		X																	
Weight	D	7.2.2.3.		X	X						X					X		X			
Performance status	D	7.2.2.4.		X	X						X					X		X			

			Screening Phase		Treatment Phase														Follow-Up		
	Category	Protocol Section	Pre-Molecular screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		EoT	30-day Safety F/U	Disease progression F/U	Survival F/U every 3 months
Day of Cycle				-28 to 1	1	2	8	15	16	22	1	2	8	15	22	1	15				
Laboratory Assessments																					
Hematology	D	7.2.2.5.1.		X	X		X	X		X	X		X	X	X	X	X up to Cycle 6 only	X			
Chemistry	D	7.2.2.5.2.		X	X		X	X		X	X		X	X	X	X	X up to Cycle 6 only	X			
Coagulation	D	7.2.2.5.3.		X																	
Urinalysis	D	7.2.2.5.4.		X	X													X			
HBV testing	D	6.3.2. 7.2.2.5.5.		X	In cases of positive HBV testing, monitor HBV-DNA every 4 weeks or every 12 weeks, per Table 6-10 and Table 6-11 (or more frequently if clinically indicated).																
HCV testing	D	6.3.2. 7.2.2.5.5.		X	In cases of positive HCV-Ab, monitor HCV-RNA every 8 weeks, per Table 6-12 (or more frequently if clinically indicated).																
Pregnancy test	D	7.2.2.5.6.		X	X						X					X		X			

			Screening Phase		Treatment Phase														Follow-Up		
	Category	Protocol Section	Pre-Molecular screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		EoT	30-day Safety F/U	Disease progression F/U	Survival F/U every 3 months
Day of Cycle				-28 to 1	1	2	8	15	16	22	1	2	8	15	22	1	15				
Imaging																					
Tumor evaluation as per RECIST 1.1 CT/MRI: - Mandatory at each evaluation: chest, abdomen - Mandatory if lesions at baseline: brain, skin - If clinically indicated: bone, other tumor sites	D	7.2.1.		X												X Every 8 wks (12 wks from C13D1)		X (if not conducted within 30 days of EOT)		X every 8 wks	
ECG (triplicate)	D	7.2.2.6.1.		X	X						X					X		X			
Safety																					
AEs	D	8.	X Procedural SAE only	X	Continuously																
Biomarkers																					
Molecular Pre-Screening (Tumor sample archival or newly obtained)		7.1.1. 7.2.4.	X																		
[redacted]																					
Whole Blood sample for determination of MET and EGFR status in cfDNA		7.2.4.		X*												X C3 and every third cycle		X			

			Screening Phase		Treatment Phase														Follow-Up		
	Category	Protocol Section	Pre-Molecular screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		EoT	30-day Safety F/U	Disease progression F/U	Survival F/U every 3 months
Day of Cycle				**-28 to 1**	**1**	**2**	**8**	**15**	**16**	**22**	**1**	**2**	**8**	**15**	**22**	**1**	**15**				
[redacted]																					
Study Drug administration	D	6.1.1.			Continuously																
PK sampling (Phase Ib part)	D	7.2.3.2.			X	X	X	X	X		X	X				X C3 and 4 only					
PK sampling (Phase II part)	D	7.2.3.3.			X	X	X				X	X				X C3 and 4 only					
Meal Recorded (Full PK participants)		6.1.1.			X						X										
Survival contact (telephone call)		7.1.6.																			X
* Collect during screening phase or at C1D1 before the first dose of study drugs is administered. [redacted]																					

Table 7-2 Visit evaluation schedule for Phase II Group 5

Period	Category	Protocol Section	Screening		Treatment – Capmatinib Monotherapy			Extension Treatment (ET) – Capmatinib + Nazartinib combination therapy			Follow-up	
Visit Name			**Molecular pre-screening**	**Screening**	**Cycle 1**	**Cycle 2 and beyond**	**EOT**	**ET-Cycle 1**	**ET-Cycle 2 and beyond**	**ET-EOT**	**30-day Safety F/U**	**Post-treatment F/U**
Day of cycle			**-**	**-28 to -1**	**1**	**1**	**-**	**1**	**1**	**-**	**-**	**-**
Obtain Molecular Pre-screening informed consent	D	7.1.1.	X									
Newly obtained tumor biopsy (preferred) or archival tumor sample for central assessment of MET amplification status		7.1.1. 7.2.4.	X[1]									
Information on prior local testing for MET amplification status		7.2.4.	X	X (only if not provided at pre-screening)								
Collection of local EGFR T790M status		7.2.4.	X									
Diagnosis and extent of cancer	D	7.1.2.2.	X									
Demography	D	7.1.2.2.	X									
Inclusion/exclusion criteria	D	5.2 5.3	X	X								

Period	Category	Protocol Section	Screening		Treatment – Capmatinib Monotherapy			Extension Treatment (ET) – Capmatinib + Nazartinib combination therapy			Follow-up	
Visit Name			**Molecular pre-screening**	**Screening**	**Cycle 1**	**Cycle 2 and beyond**	**EOT**	**ET-Cycle 1**	**ET-Cycle 2 and beyond**	**ET-EOT**	**30-day Safety F/U**	**Post-treatment F/U**
Day of cycle			**-**	**-28 to -1**	**1**	**1**	**-**	**1**	**1**	**-**	**-**	**-**
Obtain Main informed consent(s)	D	7.1.2.		X				X[2]				
IRT eligibility check	S	6.5.1.		X								
IRT Registration		6.5.1.	X	X	X	X	X	X	X	X		
Relevant medical history/current medical history	D	7.1.2.2.		X								
Prior/Concomitant Medications	D	7.1.2.2.					Continuously from 28 days prior to first dose until 30 days after last dose of study treatment				X	
Prior antineoplastic therapies	D	7.1.2.2.		X								
Smoking history	D	7.1.2.2.		X								
Targeted Physical Exam	S	7.2.2.1.			X	X	X	X	X	X		
Physical examination, including neurological exams	S	7.2.2.1.		X	As clinically indicated							
Height	D	7.2.2.3.		X								
Weight	D	7.2.2.3.		X	X	X	X	X	X	X		
Vital Signs	D	7.2.2.2.		X	X	X	X	X	X	X		
HIV history (HIV testing where locally required)	S	5.3		X								

Period	Category	Protocol Section	Screening		Treatment – Capmatinib Monotherapy			Extension Treatment (ET) – Capmatinib + Nazartinib combination therapy			Follow-up	
Visit Name			**Molecular pre-screening**	**Screening**	**Cycle 1**	**Cycle 2 and beyond**	**EOT**	**ET-Cycle 1**	**ET-Cycle 2 and beyond**	**ET-EOT**	**30-day Safety F/U**	**Post-treatment F/U**
Day of cycle			**-**	**-28 to -1**	**1**	**1**	**-**	**1**	**1**	**-**	**-**	**-**
Performance Status (ECOG)	D	7.2.2.4.		X	X	X	X	X	X	X		
Hematology	D	7.2.2.5.1		X	X	X up to Cycle 6 only	X	X	X up to ET-Cycle 6 only	X		
Chemistry	D	7.2.2.5.2.		X	X	X up to Cycle 6 only	X	X	X up to ET-Cycle 6 only	X		
Coagulation	D	7.2.2.5.3.		X (≤72 hr before C1D1)	As clinically indicated							
Urinalysis (dipstick)	D	7.2.2.5.4.		X	As clinically indicated							
HBV testing	D	6.3.2. 7.2.2.5.5.		X				In cases of positive HBV testing, monitor HBV-DNA every 4 weeks, per Table 6-10 and Table 6-11 (or more frequently if				

Period	Category	Protocol Section	Screening		Treatment – Capmatinib Monotherapy			Extension Treatment (ET) – Capmatinib + Nazartinib combination therapy			Follow-up	
Visit Name			**Molecular pre-screening**	**Screening**	**Cycle 1**	**Cycle 2 and beyond**	**EOT**	**ET-Cycle 1**	**ET-Cycle 2 and beyond**	**ET-EOT**	**30-day Safety F/U**	**Post-treatment F/U**
Day of cycle			**-**	**-28 to -1**	**1**	**1**	**-**	**1**	**1**	**-**	**-**	**-**
								clinically indicated).				
HCV testing		6.3.2. 7.2.2.5.5.		X				In cases of positive HCV-Ab, monitor HCV-RNA every 4 weeks, per Table 6-12 (or more frequently if clinically indicated).				
Pregnancy Test (Serum)	D	7.2.2.5.6.		X (≤72 hr before C1D1)			X			X		
Pregnancy Test (Urine)	D	7.2.2.5.6.				X			X			
Tumor evaluation	D	7.2.1.		X		Cycle 3 then every 8 weeks (from cycle 13 every 12 weeks)	X (Not required if previous assessment was performed ≤28 days)	X[3]	ET-Cycle 3 then every 8 weeks (from cycle 13 every	X (Not required if previous assessment was performed ≤28 days)		X every 8 weeks

Period	Category	Protocol Section	Screening		Treatment – Capmatinib Monotherapy			Extension Treatment (ET) – Capmatinib + Nazartinib combination therapy			Follow-up	
Visit Name			**Molecular pre-screening**	**Screening**	**Cycle 1**	**Cycle 2 and beyond**	**EOT**	**ET-Cycle 1**	**ET-Cycle 2 and beyond**	**ET-EOT**	**30-day Safety F/U**	**Post-treatment F/U**
Day of cycle			**-**	**-28 to -1**	**1**	**1**	**-**	**1**	**1**	**-**	**-**	**-**
									12 weeks)			
ECG (triplicate)	D	7.2.2.6.1.		X	X	As clinically indicated	X	X		X		
Adverse Events	D	8.	Continuously from signing of main ICF until 30 days after last dose of study treatment									
Serious Adverse Events	D	8.	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	
Capmatinib drug administration		6.1			Continuously twice daily dosing [b.i.d]							
Nazartinib drug administration		6.1						Continuously once daily [q.d.]				
Antineoplastic therapies since discontinuation from study treatment	D	7.1.2.2.									X	X

Period	Category	Protocol Section	Screening		Treatment – Capmatinib Monotherapy			Extension Treatment (ET) – Capmatinib + Nazartinib combination therapy			Follow-up	
Visit Name			**Molecular pre-screening**	**Screening**	**Cycle 1**	**Cycle 2 and beyond**	**EOT**	**ET-Cycle 1**	**ET-Cycle 2 and beyond**	**ET-EOT**	**30-day Safety F/U**	**Post-treatment F/U**
Day of cycle			**-**	**-28 to -1**	**1**	**1**	**-**	**1**	**1**	**-**	**-**	**-**

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 Can be collected up to C1D1

2 Each participant must sign separate combination treatment ICF prior to any assessments of the Extension Treatment period or first dose with combination therapy

3 Not required if the EOT scan is within 28 days of ET-C1D1, then the EOT scan can be defined as re-baseline of extension. Otherwise, a re-baseline scan should be arranged 28 days prior to ET-C1D1. In case exceed 28 days of C1D1 and no re-scan was done, the EOT scan can be used as re-baseline for efficacy assessment

7.1.1 Molecular pre-screening

All participants entering the pre-screening phase must sign the molecular pre-screening informed consent form (ICF).

Activating mutations L858R and ex19del

For participants in Phase Ib part and Phase II part Groups 1 3, 4 and 5 local pathology reports showing L858R and/or ex19del evidence must be available in medical records prior to sign the main ICF. Documented proof of other rare activating mutations that confer sensitivity to first and second generation EGFR inhibitors (e.g. L861Q, G719X, S768I) also satisfies eligibility criteria.

For Phase II Group 2 (de novo EGFR T790M mutation), local pathology reports showing the activating mutation analysis results must be available in the medical records as well. The participants will be enrolled irrespective of the activating mutation status, i.e. may harbor or may not harbor an EGFR activating mutation in addition to the EGFR T790M mutation.

Activating mutation status as per local pathology reports must be recorded in the eCRF for all participants.

Resistance mechanisms $EGFR^{T790M}$ and MET dysregulation: Phase Ib

In Phase Ib, if mutational status for $EGFR^{T790M}$ and MET pathway dysregulation are unknown following treatment with EGRF-TKI, a newly obtained tumor sample (preferred) or an archival tumor sample collected at or following progression on prior EGFR TKI therapy, should be provided to Novartis designated central laboratory for EGFR mutation and MET dysregulation testing.

In Phase Ib, acceptable local test results for $EGFR^{T790M}$ should be assessed using:

- In the United States with QIAGEN Therascreen EGFR test,
- In the other countries with either Roche COBAS or QIAGEN Therascreen EGFR test.

MET dysregulation should be preferably analyzed by FISH, and if sufficient tumor material is available additionally by IHC.

MET dysregulation is defined as either

- IHC 3+ (defined as ≥50% of cells staining with high intensity) and/or
- MET gene copy number ≥ 4

For Group 5: MET amplified is defined as gene copy number ≥ 5

For Phase Ib part, the participant will be able to proceed with study specific screening procedures if either

- Activating mutations L858R and/or ex19del are documented locally AND the central laboratory confirms that sufficient tumor sample has been received to perform the $EGFR^{T790M}$ mutation and/or MET dysregulation testing or

- Activating mutations L858R and/or ex19del are documented locally AND $EGFR^{T790M}$ mutational and MET statuses have been determined by the appropriate analysis methods at the local laboratory.

Resistance mechanisms $EGFR^{T790M}$ and MET dysregulation: Phase II

All participants must have sufficient tumor samples (newly obtained or archival) available for $EGFR^{T790M}$ and MET statuses determination by Novartis designated central laboratory on a biopsy collected:

- At or any time after progression on prior line of EGFR TKI for Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant);
- At any time for Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve) and Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic);
- At any time in treatment-naïve participants or at/or any time after progression on the last treatment line for advanced disease for Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic); if biopsy is not available after last treatment, the most recent available archival biopsy should be provided;
- At or any time after progression on prior line of EGFR TKI for Group 5 (EGFRmut, T790M-, MET GCN≥5, 2L, EGFR TKI resistant).

Participants in Phase II will be able to proceed with main informed consent form signature and study specific screening procedures if activating mutations L858R and/or ex19del analysis results are documented locally AND sufficient tumor samples have been submitted to the central laboratory for $EGFR^{T790M}$ and MET statuses determination.

In the Phase II, MET dysregulation is defined as either:

- IHC 3+ (defined as ≥50% of cells staining with high intensity) and/or
- MET gene copy number ≥ 4

In Phase II Group 5, MET amplified is defined as MET gene copy number (GCN) ≥ 5.

Note: Participants with prior documentation of EGFR mutation and/or MET dysregulation testing from the Novartis designated central laboratory using the same prescreening tests used in this protocol (i.e. being re-prescreened or coming from another Novartis study) are potentially eligible. Repeat tumor biopsy or additional archival tumor may not be required for these participants provided the central laboratory confirms adequate tumor tissue remains for the required study analyses.

However, if there is not enough residual tissue at the central laboratory to perform all required study analyses additional material from an archival tumor biopsy (preferably the same) will be requested.

In Phase II Group 5, MET amplification (GCN≥5) status can be determined per local laboratory result (see Section 5.2) as long as an adequate amount of tumor tissue (archived or if not available, newly obtained biopsy sample) is available at the time of enrollment for submission for retrospective central assessment of MET gene amplification status using a validated FISH test at the Novartis-designated laboratory. MET amplification testing by FISH is preferred and results from other tissue-based molecular testing methods, such as next generation sequencing

(NGS) or PCR, are accepted. Blood-based results and IHC results are not acceptable for determining MET amplification with GCN≥5. If a local result is not available, a tumor tissue sample must be submitted during pre-screening and determined as MET amplified (GCN ≥ 5) per central Novartis-designated laboratory.

MET testing may be performed while participants are still receiving anti-cancer therapy. However, the participant can only be screened for the main study once he/she has discontinued the last prior systemic treatment due to disease progression.

7.1.2 Screening

The study IRB/IEC approved main ICF must be signed and dated before any screening procedures are performed.

For all participants (except Phase II Group 5), an archival or newly obtained tumor biopsy sample will be required to be submitted to a Novartis central laboratory for genetic alterations assessment at baseline (Next Generation Sequencing [NGS] assay).

In addition, a mandatory blood sample will be collected from all participants (except Phase II Group 5), during the screening phase (or at the latest on Cycle 1 Day 1 before first study drug administration). This will be used to isolate cfDNA for assessment of EGFR mutation status.

Participants will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 7-1 and Table 7-2. Screening assessments must be repeated if performed outside of the specified screening windows (refer to Section 7.1).

The main screening period commences as soon as the participant signs the main ICF and ends when the participant fails screening or starts treatment. Evaluations will be performed within 4 weeks (i.e. within 28 calendar days) prior to the first dose of study drug, unless otherwise noted. All screening assessments, including laboratory assessments, must be performed as described in the protocol (Table 7-1 and Table 7-2). Any imaging assessments already completed as participant's standard of care within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after first dose cannot be considered baseline images. [redacted]

Screening for hepatitis B

Prior to study entry, all participants must be screened with HBV serologic markers: HBsAg, HBsAb, and HBcAb. Check HBV-DNA if HBsAg and/or HBcAb are positive. Refer to Table 6-10 for actions to be taken based on screening HBV results.

Screening for hepatitis C

Screen all participants for HC Ab. If HC Ab is detected then check HCV-RNA. Only participants who are HC Ab negative or HC Ab positive with an undetectable level of RNA are eligible to be enrolled. Note: participants with detectable HCV-RNA will not be eligible for the study. Participants with HCV-Ab positive or history of hepatitis C infection should be monitored every 8 weeks (or more frequently if clinically indicated) with HCV-RNA.

All screening evaluations will be performed within 28 days prior to Treatment Day 1. HBV/HCV tests will be performed by a local laboratory for the Phase Ib part and by a central laboratory for the Phase II part. HBV/HCV test results should be available prior to the first dose of study treatment (capmatinib + nazartinib). Participants with positive baseline hepatitis B results have to start antiviral treatment 1 to 2 weeks prior to the first dose of study treatment (capmatinib + nazartinib) and need to be monitored with HBV-DNA every 4 weeks (or more frequently if clinically indicated). Participants with HC Ab positive or history of hepatitis C infection should be monitored every 8 weeks (or more frequently if clinically indicated) with HCV-RNA.

Eligibility Check

For participants enrolled in the Phase II part of the study, once all screening procedures are completed, an eligibility checklist must be completed via IRT by the investigator or designee prior to receiving the first dose of study treatment. Please refer to and comply with the detailed guidelines in the IRT manual.

After the eligibility has been checked and confirmed that the participant is eligible for the trial, then the participant can be enrolled into the study.

A participant who has a laboratory test result or an ECG finding that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated as soon as the investigator believes the re-test result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria. If re-tests are performed during the 28-days screening period, the participant will not be required to sign another ICF, and the original participant ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed during the original screening period of 28 days, or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screen failure, and must be discontinued from the study. Participants who met all eligibility criteria but fail to be started on treatment as scheduled may also be re-screened, provided the participant was not registered previously in the CRF as having entered the Treatment Period.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed.

All required screening activities must be performed when the participant is re-screened for participation in the study. An individual participant may 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.

If a participant fails screening but is re-screened, the participant must be re-screened using the same participant number.

All eligibility criteria must be re-checked, based on the most recent data available, and met prior to enrollment of the participant into the study.

If the re-screening is successful, the following information should be collected in the CRF:

- Date the study informed consent was first signed.
- All assessments done during the first screening period.
- All assessments repeated during the re-screening period (e.g. ECG, lab).
- Updated information as per latest status during the re-screening period e.g. Medical history, diagnosis and extent of cancer.
- Adverse events based on the date of re-consent.

7.1.2.1 Information to be collected on screening failures

Participants who sign the molecular pre-screening ICF, or the molecular pre-screening ICF and the main ICF, but fail to be started on study treatment for any reason will be considered a screen failure.

The reason for molecular pre-screening failure or screening failure will be entered on the Screening Phase Disposition Page.

For all participants except particpants in Phase II Group 5, the demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure participants.

For participants in Phase II Group 5 the following eCRF pages must be completed for screening failure participants:

- EGFR and T790M status as per participant's record
- Information on prior local testing for MET amplification status (if available)
- Tumor samples collection (archival or newly obtained) for central confirmation of MET amplification status and T790M status (if local T790M status is not available)
- NSCLC diagnosis and extent of disease
- Date of diagnosis and stage of NSCLC
- Site of active disease
- Characteristics of disease
- Screening phase disposition
- Demography
- Informed consent
- Inclusion/Exclusion Criteria
- Withdrawal of consent (if applicable)
- Death (if applicable)

No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the Screening Phase (see Section 8 for SAE reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported.

7.1.2.2 Participant demographics and other baseline characteristics

Data to be collected will include general participant demographics, relevant medical history and current medical conditions, diagnosis and extent of tumor, details of prior anti-neoplastic treatments, HBV and HCV status, and any other assessments that are done for the purpose of determining eligibility for inclusion in the study. All medications and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) taken within 4 weeks prior to first dose of study drug must be recorded on the eCRF. Smoking history will be recorded on the eCRF at screening.

7.1.3 Treatment period

A treatment cycle is defined as 28 days (4 calendar weeks) for the purposes of scheduling procedures and evaluations. Please refer to Table 7-1 and Table 7-2 for details of the timing of required assessments and Section 7.1 for visit windows.

Participants will be treated until participant experiences unacceptable toxicity, progressive disease and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent/opposition to use data/biological samples as described in Section 7.1.5.

7.1.4 Discontinuation from study treatment and from study

Participants may voluntarily discontinue from the study treatment for any reason at any time. If a participant decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the participant's chart and on the appropriate CRF pages. They may be considered withdrawn/opposition to use data/biological samples, if they state an intention to withdraw/opposition to use data/biological samples, fail to return for visits, or become lost to follow-up for any other reason.

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

Discontinuation from study treatment is required under the following circumstances:

- Adverse events and laboratory abnormalities meeting criteria for study treatment discontinuation: refer to Section 6.3.
- Pregnancy
- Interruption of one of the study drugs for 21 consecutive days or more, regardless of reason for study drug interruption
- Use of prohibited treatment, refer to Appendix 4.
- Any other protocol deviation that results in a significant risk to the participant's safety.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer Section 7). In addition, before a new anti-neoplastic therapy is initiated for a participant, it is strongly recommended to perform a tumor assessment. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.7.

For Phase II, the investigator must also contact the IRT to register the participant's discontinuation from study treatment.

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

7.1.4.1 Replacement policy

Phase Ib part:

Participants will not be replaced on study. However, if a participant is considered as non-evaluable for the Dose Determining Set (DDS), enrollment of a new participant to the current cohort will be considered if there is less than the required number of evaluable participants. Enrollment of new participants may be considered until at least the minimum number (3) or at most the maximum number (6) of evaluable participants is achieved within the cohort. Minimum and maximum numbers of evaluable participants per cohort are defined in Section 6.2.3.

Phase II part:

During the Phase II part no replacements will be needed.

7.1.5 Withdrawal of informed consent/Opposition to use data/biological samples

Participants may voluntarily withdraw consent to participate in the study/make opposition to use data/biological samples for any reason at any time.

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

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 in writing (depending on local regulations) and recorded in the source documentation.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following consent withdrawal/opposition. If a participant withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Where consent to the use of Personal and Coded data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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 communication or follow up.

If the participant agrees, a final evaluation at the time of the participant's consent withdrawal/opposition should be made as detailed in the assessment table (refer to Section 7).

7.1.6 Follow-up for safety evaluations

30-day follow-up

All participants must have safety evaluations for 30 days after the last dose of investigational drug(s). At the end of this period, the investigator should assess and discuss with the participant any AE observed/concomitant medication taken since discontinuation of study treatment. This can be done via a phone contact.

Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF. Newly introduced antineoplastic therapies will be captured on the 'Antineoplastic therapies since discontinuation of study treatment' eCRF page.

Participants whose treatment is permanently discontinued due to an AE (clinical or based on abnormal laboratory value) must be followed until resolution or stabilization of the event, whichever comes first. In case of an abnormal laboratory value, blood tests should be repeated until resolution or stabilization.

Post-treatment follow-up

Any participant who discontinues from study treatment for any reason (except for death, disease progression, lost to follow-up, consent withdrawal/opposition or study termination) will continue to have tumor assessments performed every 8 weeks in the follow-up period until disease progression, death, lost to follow-up, end of study (Last Patient Last Visit, see Section 4.3), or withdrawal of consent/opposition to use data/biological samples.

Antineoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

Survival follow-up

Upon completion of the 30-day follow-up or disease progression follow-up, all participants except those who withdrew consent for follow-up as a result of participant decision, or were lost to follow-up, will be followed for survival every 3 months (telephone call) until death or until the end of the study (Last Patient Last Visit, see Section 4.3). Participant's survival status may be collected via a phone call.

This visit does not apply for participants in Phase II Group 5.

7.1.7 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw

consent /oppose to the use of their data/biological samples, the investigator should show "due diligence" by contacting the participant, family or family physician as agreed in the informed consent and 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 lost to follow-up until due diligence has been completed. Participants lost to follow-up should be recorded as such on the appropriate Disposition eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be determined locally according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Appendix 1).

Tumor response evaluations will be determined by the local investigators, based on RECIST 1.1. Imaging data will be centrally collected, checked for quality and stored for possible independent review by an imaging CRO designated by Novartis. Independent tumor response evaluations would then be determined according to the Novartis guideline (Appendix 1), based on RECIST 1.1. For Groups 1 to 4, the results of the central BIRC evaluations may be used for secondary analyses purposes.

CT/MRI scans will be performed at baseline within 28 days (preferably 7 days) before start of treatment and subsequently every 8 weeks from start of Cycle 3 until progression of disease and every 12 weeks from Cycle 13 Day 1 until progression of disease. See Table 7-3 for details. CT/MRI scan will be performed at EOT if not conducted within 30 days prior to EOT. Disease progression follow-up should be performed as described in Section 7.1.6. Depending on regulatory requirements it is allowed to have the EOT scan performed within an extended time frame but not later than 8 weeks from the last CT scan.

For participants in Phase II Group 5 entering the extension treatment period, a new baseline assessment should be performed no more than 28 days before the start of combination therapy. If the scan confirming disease progrogression on capmatinib monotherapy occurs within 28 days of the first dose of combination therapy, this scan may be used as the baseline scan for combination therapy.

After baseline, all assessments should be performed within ±7 days of the scheduled day of assessment. Imaging evaluations subsequent to an off-schedule confirmatory scan should be performed according to the original assessment schedule. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow up.

If at baseline a participant has a medical contraindication to CT i.v. contrast or develops a contraindication during the trial, a non-contrast CT of chest plus contrast-enhanced MRI of abdomen is acceptable.

Participants with clinical evidence of bone metastases must have a whole body bone scan at baseline per local institutional practice (e.g., Tc99m bone scan, NaF positron emission tomography (PET) or whole body bone MRI). Lesions identified on the whole body bone scan at baseline, which are not visible on the chest and abdomen CT (or MRI) scan should be imaged

at baseline and followed at subsequent scheduled visits using localized CT, MRI or X-ray. After baseline, whole body bone scans need not be repeated, unless clinically indicated.

Skin lesions present at baseline should be documented using color photography, including a ruler, so that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

Baseline brain CT or MRI will be mandated for all participants prior to study treatment. Subsequent brain scans should only be conducted if brain lesions are documented at baseline for eligible participants or in participants that develop symptoms indicative of brain metastases.

All CRs and PRs must be confirmed by a second assessment not earlier than 4 weeks after the criteria for response are first met.

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.

PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media.

All participants discontinuing from the study for PD must have their disease progression documented by radiologic evaluation. In cases of clinically-evident disease progression, all efforts should be made to perform a radiologic evaluation.

Participants with symptoms of rapidly progressing disease without radiological evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or participant discontinued due to ‘Disease progression’ or death due to study indication.

Table 7-3 Imaging collection plan

Procedure	Screening/ Baseline	During Treatment/Follow-up	EoT/ Re-baseline
CT or MRI with contrast enhancement (Chest and Abdomen)	Mandated	Mandated, every 8 weeks (±7 days) Every 12 weeks (±7 days) from Cycle 13 Day 1.	>28 days from last assesment
Whole body bone scan	If clinically indicated	If clinically indicated	If bone metastasis is clinically suspected
Brain CT or MRI	Mandated	If brain positive at screening every 8 weeks (±7 days) Every 12 weeks (±7 days) from Cycle 13 Day 1. If brain negative at screening, as clinically indicated.	If brain positive at screening Or as clinically indicated if brain negative
Bone X-ray, CT or MRI (bone lesions only)	If lesions on bone scan that are not visible on the chest and abdomen CT/MRI	If bone lesions at screening every 8 weeks (±7 days) Every 12 weeks (±7 days) from Cycle 13 Day 1.	If lesions not visible on CT/MRI chest and abdomen

Procedure	Screening/ Baseline	During Treatment/Follow-up	EoT/ Re-baseline
Skin color photography (skin lesions only)	Mandated if skin lesions at screening	If skin lesions at screening every 8 weeks (±7 days) Every 12 weeks (±7 days) from Cycle 13 Day 1.	If skin lesions present
CT or MRI of other tumor sites (e.g., pelvis)	If clinically indicated	If lesions identified at screening every 8 weeks (±7 days) Every 12 weeks (±7 days) from Cycle 13 Day 1.	If clinically indicated

As per Section 2.7, 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, changes in collection of images (e.g., change of facility or frequency) can be listed as one of the risk mitigation procedures.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, height, weight, ECOG performance status, laboratory evaluations, 12-lead ECG as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

As per Section 2.7, 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 4 weeks (+/- 1 week) 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.

7.2.2.1 Physical examination

A complete physical examination will be performed as per Table 7-1 and Table 7-2 and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information about the physical examination must be present in the source documentation.

A short physical examination, including examination of general appearance as well as organ or complaint-specific, will be performed at all visits starting from Cycle 5 Day 1.

For participants in Phase II Group 5, a targeted physical examination will be performed at all visits as indicated in Table 7-2 and during treatment except where a complete physical examination is required (see above). It will include at least the examination of general appearance and vital signs (respiratory rate, blood pressure [SBP and DBP] and pulse). If indicated based on symptoms, additional examinations 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 metastasis neurological status will also be evaluated at the time of radiological assessments.

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

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before dosing and as indicated in Table 7-1 and Table 7-2 as per institutional standards.

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

Unscheduled assessment can be performed if clinically indicated.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured as indicated in Table 7-1 and Table 7-2.

Height information will be collected at screening only.

7.2.2.4 Performance status

The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale as specified in Table 7-1, Table 7-2 and Table 7-4.

Table 7-4 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

7.2.2.5 Laboratory evaluations

For the Phase Ib part, all laboratory parameters assessed for safety purposes will be evaluated locally, at the site. Refer to Table 7-5 for a summary of the parameters to be evaluated according to Table 7-1. **For Phase II Group 5**, all laboratory analysis will be performed locally, inclusive of assessment for participants' eligibility. The frequency of the assessments is indicated in Table 7-1 for the Phase Ib part and Table 7-2 for Phase II Group5.

Unscheduled assessment can be performed if clinically indicated.

For the Phase II part (Groups 1 to 4), central laboratories will be used for the analysis of scheduled hematology, biochemistry and other blood specimens collected as part of safety monitoring (as detailed in Table 7-5). The frequency of the assesments is indicated for the Phase II part (Groups 1 to 4) in Table 7-1. Dipstick urinalysis will be performed locally, except in the

case of any significant findings, a urine sample will be sent to central laboratory for further microscopic analysis. Laboratory values obtained prior to treatment from central laboratory will be used to assess participant's eligibility. Only laboratory results from the central laboratory can be used to determine participant's eligibility for the study. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 7.1).

Local laboratory assessments may be performed 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 eCRF as unscheduled visit if the following criteria are met:

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

Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in a separate [Laboratory Manual].

As per Section 2.7, 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 and protocol specified safety laboratories assessments, an alternative laboratory (local) collection site may be used.

Table 7-5 Central/local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, platelets, red blood cells (RBC), white blood cells (WBC), WBC morphology with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), amylase, lipase, calcium, chloride, magnesium, potassium, creatinine, creatinine clearance, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total protein, blood urea nitrogen or urea, uric acid, glucose, GGT
Urinalysis	Dipstick/bedside measurements for specific gravity, pH, protein, glucose, bilirubin, ketones, leukocytes, and blood will be performed. Any clinically significant findings on dipstick will be followed up with a microscopic evaluation.
Coagulation	Prothrombin time (PT) or international normalized ratio (INR),
HBV and HCV	HBsAg, HBsAb, HBcAb, HBV-DNA, HC Ab, HCV-RNA

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

7.2.2.5.2 Clinical chemistry

Clinical chemistry panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

7.2.2.5.3 Coagulation

Coagulation panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

7.2.2.5.4 Urinalysis

Urinalysis panel outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

7.2.2.5.5 HBV and HCV testing

HBV tests outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

HCV tests outlined in Table 7-5 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

7.2.2.5.6 Pregnancy and assessments of fertility

At screening (and/or Cycle 1 Day 1) a serum pregnancy test should be performed within 72 hours before the first dose, 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 the Phase II part, serum pregnancy tests will be performed centrally. Urine pregnancy tests will be performed locally.

As per Section 2.7, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, the supply of 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. If the test result is positive, the participant should stop the intake of study drug and inform the investigator. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following Country specific measures).

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard 12 lead ECGs will be performed as per the assessment schedule in Table 7-1, Table 7-2 and Table 7-6.

Triplicate ECGs will be performed at all time-points during the trial.

Table 7-6 Local 12-lead ECG collection plan

Cycle (or visit)	Day	Time	Technique
Screening	-	Anytime	Triplicate 12 Lead
1	1	Pre-dose	Triplicate 12 Lead
1	1	2 hr post-dose (within 1 hour of post-dose PK sample)*	Triplicate 12 Lead
2	1	Pre-dose	Triplicate 12 Lead
2	1	2 hr post dose (within 1 hour of post-dose PK sample)*	Triplicate 12 Lead
3 and afterwards	1	Pre-dose	Triplicate 12 Lead
EOT	-	Anytime	Triplicate 12 Lead
Unscheduled		Anytime	Triplicate 12 Lead
*: not applicable for Phase II Group 5			

The 3 ECGs may be performed with an interval of 5-10 min or according to local practices. Participant's eligibility should be determined based on the average of the 3 ECGs measures.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. 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 when the participant signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.2.3 Pharmacokinetics

Serial blood samples will be collected from all participants for the analysis of capmatinib, nazartinib, and LMI258 (nazartinib metabolite) plasma concentration. The PK analysis will be performed according to Section 10.6.3.

[redacted]

Note that for participants in Phase II Group 5, no PK blood samples will be collected.

7.2.3.1 Pharmacokinetic blood collection and handling

The exact date and clock times of drug administration and PK blood draw will be recorded on the appropriate eCRF. The timing of meals, before and after the dose on days when PK samples are drawn, should be recorded in the source documents. If vomiting occurs within 4 hours following capmatinib (and nazartinib) administration on the day of post dose PK blood sampling, the clock time of vomiting should be recorded on the Dose Administration Record PK eCRF page.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. At specified time points, 4 mL blood will be collected. Refer to the [CINC280X2105C Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

7.2.3.2 Pharmacokinetic sampling during Phase Ib dose escalation part

Full PK blood samples for capmatinib, nazartinib and metabolite LMI258 will be collected on Days 1, 2, 15 and 16 of Cycle 1, and Days 1 and 2 of Cycle 2 during the Phase Ib dose escalation part (please refer to Table 7-7). Pre-dose blood PK samples will be collected on Day 8 of Cycle 1, Day 1 of Cycle 3 and Cycle 4.

Table 7-7 Schedule of blood sample collections for capmatinib, nazartinib, and metabolite LMI258 PK assessment during Phase Ib dose escalation part

Dose reference ID [a] (capmatinib)	Dose reference ID [a] (nazartinib)	PK Sample number (capmatinib)	PK Sample number (nazartinib)	Cycle	Day	Scheduled time (hours)
1	21	1	101	1	1	0 hr / pre-dose [b]
1	21	2	102	1	1	0.5 hr (±10 minutes)
1	21	3	103	1	1	1 hr (±10 minutes)
1	21	4	104	1	1	2 hr (±10 minutes)
1	21	5	105	1	1	4 hr (±15 minutes)
1	21	6	106	1	1	8 hr (±1 hr)
1/2	21	7	107	1	1	12 hr (± 1 hr)
2/101	21/201	8	108	1	2	0 hr / pre-C1D2 dose [b]
3	22	9	109	1	8	0 hr / pre-C1D8 dose
4	23	10	110	1	15	0 hr / pre-C1D15 dose [b]
4	23	11	111	1	15	0.5 hr (±10 minutes)
4	23	12	112	1	15	1 hr (±10 minutes)
4	23	13	113	1	15	2 hr (±10 minutes)
4	23	14	114	1	15	4 hr (±15 minutes)
4	23	15	115	1	15	8 hr (±1 hr)
4/5	23	16	116	1	15	12 hr (± 1 hr)
5/102	23/202	17	117	1	16	0 hr / pre-C1D16 dose [b]
6	24	18	118	2	1	0 hr / pre-C2D1 dose [b]
6	24	19	119	2	1	0.5 hr (±10 minutes)
6	24	20	120	2	1	1 hr (±10 minutes)
6	24	21	121	2	1	2 hr (±10 minutes)
6	24	22	122	2	1	4 hr (±15 minutes)

Dose reference ID [a] (capmatinib)	Dose reference ID [a] (nazartinib)	PK Sample number (capmatinib)	PK Sample number (nazartinib)	Cycle	Day	Scheduled time (hours)
6	24	23	123	2	1	8 hr (±1 hr)
6/7	24	24	124	2	1	12 hr (± 1 hr)
7/103	24/203	25	125	2	2	0 hr / pre-C2D2 dose [b]
8	25	26	126	3	1	0 hr / pre-C3D1 dose [b]
9	26	27	127	4	1	0 hr / pre-C4D1 dose [b]
--		1001+[c]	2001+[c]	NA	NA	Unscheduled

[a] The first dose reference ID is for last dose the participant received prior to the collection of the PK sample, while the second dose reference ID is for current dose

[b] Take samples immediately prior to the administration of nazartinib and capmatinib

[c] Unscheduled blood samples will be uniquely, sequentially numbered 1001, 1002, … or 2001, 2002, …

7.2.3.3 Pharmacokinetic sampling during Phase II part

Full PK blood samples for capmatinib, nazartinib and metabolite LMI258 (nazartinib metabolite) will be collected on Days 1, and 2 of Cycle 1 and Cycle 2 during the Phase II part for the first 10 participants dosed in Group 3 (first line) and for approximately 20 participants in Group 4 (please refer to Table 7-.8). Pre-dose blood PK samples will be collected on Day 8 of Cycle 1, Day 1 of Cycle 3 and Cycle 4. No PK blood samples will be collected for participants in Group 5.

If a participant experiences an adverse event that fits the criteria of a SAE or DLT as determined by the Investigator, an unscheduled PK blood sample should be collected for measurement of plasma drug concentrations, unless the event occurs on the day of planned PK profile sampling collection.

Table 7-8 Schedule of blood sample collections for capmatinib, nazartinib and LMI258 PK assessment during Phase II part (first 10 participants dosed in Group 3 and approximately 20 participants in Group 4)

Dose reference ID [a] (capmatinib)	Dose reference ID [a] (nazartinib)	PK Sample number (capmatinib)	PK Sample number (nazartinib)	Cycle	Day	Scheduled time (hours)
11	31	201	301	1	1	0 hr / Pre-dose [b]
11	31	202	302	1	1	0.5 hr (±10 minutes)
11	31	203	303	1	1	1 hr (±10 minutes)
11	31	204	304	1	1	2 hr (±10 minutes)
11	31	205	305	1	1	4 hr (±15 minutes)
11	31	207	307	1	1	8 hr (±1 hr)
11/12	31	207.5	307.5	1	1	12 hr (±1 hr)
12/110	31/210	208	308	1	2	0 hr / pre-C1D2 dose [b]
113/13	132/32	209	309	1	8	0 hr / pre-C1D8 dose
114/14	133/33	210	310	2	1	0 hr / pre-C2D1 dose [b]
14	33	211	311	2	1	0.5 hr (±10 minutes)
14	33	212	312	2	1	1 hr (±10 minutes)
14	33	213	313	2	1	2 hr (±10 minutes)
14	33	214	314	2	1	4 hr (±15 minutes)
14	33	216	316	2	1	8 hr (±1 hr)
14/15	33	216.5	316.5	2	1	12 hr (±1 hr)
15/120	33/220	217	317	2	2	0 hr / pre-C2D2 dose [b]
116/16	134/34	218	318	3	1	0 hr / pre-C3D1 dose [b]
117/17	135/35	219	319	4	1	0 hr/ pre-C4D1 dose [b]
--		3001+[c]	4001+[c]	NA	NA	Unscheduled

[a] The first dose reference ID is for last dose the participant received prior to the collection of the PK sample, while the second dose reference ID is for current dose

[b] Take samples immediately prior to the administration of nazartinib and capmatinib

[c] Unscheduled blood samples will be uniquely, sequentially numbered 3001, 3002, … or 4001, 4002, …

Sparse PK samples will be collected from the rest of the participants during Phase II part on Days 1, and 2 of Cycle 1 and Cycle 2 to assess single dose and steady-state plasma PK of capmatinib, nazartinib and metabolite LMI258. Please refer to Table 7-9 for PK collection schedule. The data may be used in conjunction with samples from dose escalation as part of a population pharmacokinetic assessment.

Table 7-9 Schedule of blood sample collections for capmatinib, nazartinib and LMI258 PK assessment during Phase II part (rest of Group 3 and Group 4 participants)

Dose reference ID [a] (capmatinib)	Dose reference ID [a] (nazartinib)	PK Sample number (capmatinib)	PK Sample number (nazartinib)	Cycle	Day	Scheduled time (hours)
11	31	201	301	1	1	0 hr / pre-dose/0 hr [b]
11	31	204	304	1	1	2 hr (±10 minutes)
11	31	206	306	1	1	6 hr (±15 minutes)
12/110	31/210	208	308	1	2	0 hr/pre-C1D2 dose [b]
113/13	132/32	209	309	1	8	0 hr / pre-C1D8 dose
114/14	133/33	210	310	2	1	0 hr / pre-C2D1 dose [b]
14	33	213	313	2	1	2 hr (±10 minutes)
14	33	215	315	2	1	6 hr (±15 minutes)
15/120	33/220	217	317	2	2	0 hr / pre-C2D2 dose [b]
116/16	134/34	218	318	3	1	0 hr / pre-C3D1 dose [b]
117/17	135/35	219	319	4	1	0 hr / pre-C4D1 dose [b]
--		3001+[d]	4001+[d]	NA	NA	Unscheduled

[a] The first dose reference ID is for last dose the participant received prior to the collection of the PK sample, while the second dose reference ID is for current dose
[b] Take samples immediately prior to the administration of nazartinib and capmatinib
[c] Unscheduled blood samples will be uniquely, sequentially numbered 3001, 3002, …, or 4001, 4002, …

7.2.3.4 Analytical method

Capmatinib, nazartinib, and LMI258 concentrations in human plasma will be determined with a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Any results below the lower limit of quantification (LLOQ) of 1.0 ng/mL and any missing samples will be labeled accordingly.

7.2.3.5 Unscheduled pharmacokinetic sampling

If participant experiences an AE that fits the criteria of a SAE or DLT as determined by the Investigator, an unscheduled PK blood sample should be collected for the measurement of capmatinib, nazartinib and LMI258 plasma drug concentrations.

7.2.4 Biomarkers

[redacted]

Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the [CINC280X2105C Laboratory Manual]. The sample collection information as required should be recorded on the eCRF page(s) and central laboratory requisition form(s).

As per Section 2.7, 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, changes in blood and tumor samples collection for biomarkers analysis can be listed as one of the risk mitigation procedures.

7.2.4.1 Biomarker assessments in tumor

At time of pre-screening, all participants must have sufficient tumor samples (archival or newly obtained) submitted for resistance mechanisms evaluation by Novartis designated central laboratory. In Phase II Group 5, MET amplification (GCN≥5) status can be determined based on local results, however a mandatory biopsy sample must be submitted at screening for retrospective central assessment at the Novartis-designated central laboratory. The requirements for local and central assessments of biomarkers in tumor during the molecular pre-screening are described in Sections 5.2 and Section 7.1.1.

Newly obtained biopsy is defined as biopsy collected upon signature of the relevant ICF.

[redacted]

Assessment of MET and EGFR status in cfDNA samples

This is not applicable for participants in Phase II Group 5.

Blood samples will be collected from all participants during the screening phase or at the latest at C1D1 (pre-dose), Cycle 3 Day 1, and at Day 1 of every third subsequent cycle (i.e. C6D1, C9D1, etc.), and at EOT for isolation of cell free DNA (cfDNA). Isolated cfDNA will be assessed for MET amplification and EGFR mutation status. [redacted]

Table 7-10 Biomarker sample collection plan in the Phase Ib

Type of analysis	Visit	Mandatory /Optional	Local/ Central analysis	Methods	Material	Volume
Active EGFR Mut. L858R or ex19Del	Pre-screening	Mandatory	Local	Any methods	Biopsy collected at any time	N/A
MET	Pre-screening	Mandatory	Local	FISH or IHC Any methods	Biopsy collected at or any time after progression on first or second generation EGFR TKI	N/A
			Central	FISH and/or-IHC	IF NO LOCAL RESULTS AVAILABLE. Biopsy collected at or any time after progression on first or second generation EGFR TKI Either newly obtained formalin-fixed biopsy (preferred) or archival tumor block or slides of a formalin fixed paraffin embedded (FFPE)	Block or 5 slides
EGFR T790M	Pre-screening	Mandatory	Local	Qiagen therascreen OR Roche Cobas (all countries except USA)	Biopsy collected at or any time after progression on first or second generation EGFR TKI	N/A
			Central	PCR	IF NO LOCAL RESULTS AVAILABLE. Biopsy collected at or any time after progression on first or second generation EGFR TKI. Preferably same specimen than for MET.	6 slides (unless block submitted for pre-screening)
[redacted]						

Type of analysis	Visit	Mandatory /Optional	Local/ Central analysis	Methods	Material	Volume
[redacted]						
cell free DNA	• Screening or C1D1 (pre-dose) • C3D1 and every third cycle • EOT	Mandatory	Central	PCR, NGS and/or other methods	Blood sample	2 x 10 mL
[redacted]						

N/A: not applicable

Table 7-11 Biomarker sample collection plan in the Phase II

Type of analysis	Visit	Mandatory /Optional	Local/ Central analysis	Methods	Material	Volume
Activ. EGFR Mut. L858R or Ex19Del	Pre-screening	Mandatory	Local	Any methods	Biopsy collected at any time	N/A
MET	Pre-screening	Mandatory	Central (Group 5: If local results available, retrospective central MET confirmation is required; if local results not available, central MET testing is required)	FISH and/or IHC Group 5: Local molecluar test for MET amplification of GCN ≥ 5 (IHC not permitted)	- Group 1: biopsy collected at or any time after progression on last EGFR TKI line. - Groups 2 and 3: biopsy collected at any time. - Group 4: biopsy collected at any time (if treatment-naïve) or at/or any time after progression on last antineoplastic treatment (if 2/3L participants); if biopsy is not available after last treatment, the most recent available archival biopsy should be provided. Either newly obtained formalin-fixed biopsy (preferred) or archival tumor block or slides of a formalin fixed paraffin embedded (FFPE) Group 5: Biopsy collected at or any time after progression on prior line of EGFR TKI	Block or 5 slides
EGFR T790M	Pre-screening	Mandatory	Central (local results acceptable in Group 5)	PCR	- Group 1: biopsy collected at or any time after progression on last EGFR TKI line. - Groups 2 and 3: biopsy collected at any time. - Group 4: biopsy collected at any time (if treatment-naïve) or at/or any time after progression on last antineoplastic treatment (if 2/3L participants); if biopsy is not available after last treatment, the most recent available archival biopsy should be provided. Preferably same specimen than for MET. Group 5: At or any time after progression on prior line of EGFR TKI (if local result available, submit at screening or C1D1)	6 slides (unless block submitted for pre-screening)
Retrospective MET	Screening or C1D1 (pre-dose)	Mandatory	Central (Group 5 only: if local results available)	FISH or other methods	For Group 5 only: IF LOCAL RESULTS AVAILABLE. Biopsy collected at or any time after progression on first or second generation EGFR TKI.	Block or 5 slides

Type of analysis	Visit	Mandatory /Optional	Local/ Central analysis	Methods	Material	Volume
[redacted]						

Type of analysis	Visit	Mandatory /Optional	Local/ Central analysis	Methods	Material	Volume
cell free DNA	Screening or C1D1 (pre-dose) C3D1 and every third cycle EOT	Mandatory	Central	PCR, NGS and/or other methods	Blood sample Not applicable for Group 5	2 x 10 mL
[redacted]						

[redacted]
N/A: not applicable

8 Safety monitoring, reporting and committees

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event 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 whose EGFR and/or MET statuses are unknown and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related 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 in the Adverse Event CRF.

Participants whose EGFR mutation and MET statuses are known will sign the main study ICF.

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

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

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

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study (but is collected as a seriousness criterion); rather, information about deaths will be collected though a Death form.

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 (participant) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event must be recorded under the signs, symptoms, or diagnosis associated with them, accompagnied by the following information:

a. The severity grade (CTCAE Grade 1-4)
b. Its duration (Start and end dates) and the outcome must be reported
c. Its relationship to the study treatment and other investigational 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.
d. Action taken with respect to study or investigational treatment (dose not changed, dose Reduced/increased, drug interrupted/permanently discontinued)
e. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
f. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
g. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met.

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

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (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 study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), 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 (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 Investigator's Brochure (IB).

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

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

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the [capmatinib Investigator's Brochure] and [nazartinib Investigator's Brochure].

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,

Note that hospitalizations for the following reasons should not be reported as serious adverse events:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

- Social reasons and respite care in the absence of any deterioration in the participant's general condition

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 SAE Reporting

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

Serious adverse events considered by the investigator to be possibly related to a biopsy procedure will be indicated as such in the AE eCRF. This information will be followed-up for 30 days after the biopsy procedure.

For participants with known EGFR and/or MET statuses who sign the main study ICF, SAE collection starts at time of main study informed consent whether the participant is a screen failure or not.

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the participant has stopped study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: if more stringent, local regulations regarding reporting timelines prevail).

Any SAEs experienced after this 30 days period (or 5 half-lives, whichever is longer) should only be reported to Novartis safety if the investigator suspects a causal relationship to the study treatment, unless otherwise specified by local law/regulations. Recurrent episodes, complications, or progression of the initial SAE 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 should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form immediately, without undue delay, but under no circumstances later than within 24 hours obtaining knowledge of the events to Novartis safety (Note: if more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

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

If the SAE is not previously documented in the [capmatinib Investigator's Brochure] and [nazartinib Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO & PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancy reporting

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 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 investigational treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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.

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [capmatinib Investigator's Brochure] and [nazartinib Investigator's Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator

Notifications. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed.

8.5 Data Monitoring Committee

An independent data monitoring committee will not be formed for this study.

For the Phase Ib part of the study

Novartis will host investigator teleconferences on a regular basis during the study. Further, Novartis and the investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose escalation teleconference the clinical course (safety information including both DLTs and all CTCAE Grade 2 or higher toxicity data during the first cycle of treatment, and PK data) for each participant in the current dose cohort will be described in detail. Updated safety data on other ongoing participants, including data in later cycles, will be discussed as well.

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of participants will be guided by the BLRM's (with EWOC) recommendation, and a medical review of relevant clinical, PK and laboratory data. Novartis and the investigator parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or recruit an additional cohort of participants at the current dose level (see).

Phase II part of the study

This is a single arm trial (i.e. no comparator arm) and there is no a priori information as per the FDA Guidance of "situations in which safety concerns may be unusually high" or the participant population being studied are "potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity." Thus, an independent data monitoring committee will not be constituted for the Phase II part of this study.

The Novartis clinical team will review the safety data on a regular basis. A review of the safety data and assessment of futility, based on the calculated Bayesian probability of success (PoS) will be performed at the interim analysis of Group 3 (first line) by the Novartis clinical trial team and shared with the investigators in a data review meeting.

At the time of the interim analysis for Group 3, the best overall response for each participant will be derived from the overall lesion response assessments performed by the Investigator. These will be used to calculate the overall response rate for the respective group and a Bayesian analysis will be performed to estimate the PoS of the trial given the current data (see Section 10.9 for details).

It is envisioned that the team may make three types of recommendations at the interim analysis, namely:

- No safety or efficacy issues, ethical to continue the study group as planned
- PoS is too small and the study group is terminated due to lack of significant activity
- Serious safety concerns precluding further treatment in the study group, regardless of efficacy.

At the time of the interim analysis for Group 5, the response for each participant will be derived from the overall lesion response assessments performed by the Investigator. These will be used to calculate the ORR and a Bayesian analysis will be performed to estimate the POS of the trial given the current data (see Section 10.9 for details).

9 Data collection and database management

9.1 Data confidentiality

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

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

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

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

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

9.2 Site monitoring

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

The investigator must maintain source documents for each 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 recorded on CRFs must be traceable to source documents in the participant's file. The investigator must also keep the original signed informed consent form (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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using EDC, the designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator staff.

In addition, data entered into the IRT for drug assignment and participant identifiers (i.e. date of birth, gender and participant’s ID) will be transferred electronically to Novartis as described in the Data Transfer Specifications for the designated IRT vendor.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

PK and those applicable biomarker samples, clinical laboratory samples and imaging data will be processed centrally and the results will be sent electronically to Novartis.

For EDC studies, after database lock, the investigator will receive copies of the participant data for archiving at the investigational site. Data collected by the third parties (such as imaging, safety laboratories, biomarkers and PK) will be sent electronically to Novartis.

For Phase II participants, data about all study treatments dispensed to the participant and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The

system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel.

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.

10 Statistical methods and data analysis

Study data will be analyzed by Novartis and/or a designated contract research organization (CRO). Any data analysis carried out independently by the investigator must be submitted to Novartis before publication or presentation.

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and pharmacokinetics measurements. Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data summary statistics including mean, standard deviation, median, minimum, and maximum will be presented. In addition, individual listings of all raw data captured in the clinical database will be presented by treatment group and participant. All data from participating centers in this protocol will be combined, so that an adequate number of participants will be available for analysis.

The following rules will be followed for reporting results unless stated otherwise:

- **Phase Ib part:** Participants treated during the dose escalation with the same initial dose level and schedule of nazartinib and of capmatinib will be pooled into a single treatment group. All summaries, listings, figures and analyses will be performed by treatment group (unless otherwise specified)
- **Phase II part:** Participants will be reported according to the group to which they were assigned at baseline based on their mutation status and prior lines of systemic antineoplastic therapies. All summaries, listings, figures and analyses will be performed by group. The primary analysis for the groups 1 to 4 will be performed when participants enrolled in each respective group have completed at least 6 cycles of treatment or discontinued prior to that time. Any additional data for participants continuing to receive study treatments past the data cut-off date for the primary analysis in each of the groups will be reported in an interim CSR when all participants from Phase Ib and Groups 1 to 4 have discontinued the study. Note: due to mutation rarity and to allow for enrollment completion within a reasonable timeframe, enrollment in the Phase II Group 2 will stop once recruitment is completed in the other Phase II groups.
  The primary analysis for Group 5 will be performed when participants in the group have completed at least 6 cycles of capmatinib monotherapy or discontinued capmatinib monotherapy prior to that time. If participants are ongoing at that time, a further final CSR might be prepared.

Information on modified or missed visits or assessments during a public health emergency as declared by local or regional authorities (see Section 2.7), i.e., pandemic, epidemic or natural disaster, will be collected to assess the impact on the analysis.

10.1 Analysis sets for Phase Ib and Phase II Groups 1 to 4

The following analysis sets which will be derived prior to database lock will be used. If required, additional analysis sets will be defined in the Statistical Analysis Plan (SAP).

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all participants who have received at least one dose of either capmatinib or nazartinib. Participants will be analyzed according to the planned treatment they have been assigned to. The FAS will be used for all listings of raw data.

10.1.2 Safety Set

The Safety Set includes all participants who received at least one dose of study treatment (i.e. at least one dose of any component of the study treatment). Participants will be analyzed according to the study treatment (regimen) they actually received. A precise definition of "actually received" will be added in the Statistical Analysis Plan (SAP).

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) will consist of a subset of participants from the FAS who have an adequate tumor assessment at baseline, are evaluable for efficacy, and no major protocol deviations. A participant will be considered evaluable for efficacy if they have at least one post baseline response not assessed as 'unknown' or 'not assessed'.

All major protocol deviations leading to exclusion from the PPS will be detailed in the SAP.

Participants will be classified according to treatment as assigned.

The PPS will be used in the Phase II part of the study only and will define the participants used in the sensitivity analysis of the primary endpoint (see). If the PPS and the FAS are identical, then analyses described using the PPS below will not be performed.

10.1.4 Dose-determining set

The DDS consists of all participants from the safety analysis set in the Phase Ib dose escalation part who either meet the minimum exposure criterion and have sufficient safety evaluations, or have experienced a DLT during Cycle 1. This constitutes an evaluable participant for the determination of MTD.

A participant is considered to have met the minimum exposure criterion if he/she has received at least 75% of the planned doses of nazartinib and of capmatinib in the first 28 days of dosing, i.e. at least 21 out of the 28 full planned daily doses of nazartinib (q.d.) and at least 21 out of the 28 full planned daily doses of capmatinib (b.i.d.). Participants who do not experience DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for $\geq$ 28 days following the first dose, and are considered by both Novartis and Investigators to have enough safety data to conclude that a DLT did not occur.

10.1.5 Pharmacokinetic analysis set for capmatinib /nazartinib

The pharmacokinetic analysis set (PAS) for capmatinib (for nazartinib, and for LMI258, respectively) includes all participants who provide at least one evaluable PK concentration.

For a PK concentration to be evaluable, all of the following conditions need to be met:

- Participants have taken at least one planned dose of capmatinib and nazartinib
- For PK samples taken on or after Cycle 1 Day 8, participants have taken the planned dose of capmatinib and nazartinib, for at least 3 consecutive days prior to sampling for capmatinib and for at least 5 consecutive days prior to sampling for nazartinib
- Participants haven't vomited within 4 hours after the dosing of capmatinib (respectively nazartinib) on PK sample collection days
- For pre-dose samples on or after Cycle 1 Day 8, have the pre-dose sample collected before the next dose administration and 9 to 15 hours after the last dose administration of capmatinib and 20 to 28 hours after the last dose administration of nazartinib Note: the second part of the condition (at least 9 to 15 hours, at least 20 to 28 hours, respectively) can only be evaluated for Phase II participants due to data collection problems in Phase Ib.
- Participant did not take prohibited medicines that could affect capmatinib or nazartinib PK/exposure
- Participant took capmatinib and nazartinib under the assigned prandial conditions **on PK sample collection days**

The PAS will be used for summaries of PK concentration data, and PK parameters.

10.1.6 Full pharmacokinetic analysis set for capmatinib /nazartinib

The Full pharmacokinetic analysis set (Full PAS) for capmatinib (for nazartinib and for LMI258, respectively) includes all PAS participants for capmatinib (for nazartinib and for LMI258, respectively) who provide at least one evaluable PK profile for capmatinib (respectively nazartinib).

A PK profile is considered evaluable for capmatinib (for nazartinib and for LMI258 respectively) if all of the following conditions are satisfied:

- Participant received at least one dose of the planned treatments of capmatinib and nazartinib
- Participant provided at least one valid primary PK parameter (AUCtau or Cmax) on either Cycle 1 Day 1, Cycle 1 Day 15 (as applicable) or Cycle 2 Day 1

PK parameters of capmatinib, nazartinib, or LMI258 may be excluded on an individual basis depending on the evaluation of the concentration-time profile. These participants will be identified by the clinical pharmacologist at the time of analysis and the reason for such exclusions will be provided.

10.2 Analysis sets for Phase II Group 5

10.2.1 Full Analysis Set

The Full Analysis Set comprises all participants enrolled into Group 5 who have been treated with at least one dose of capmatinib monotherapy. Demographics and other baseline characteristics will be summarized based on the FAS.

10.2.2 Evaluable Analysis Set

The Evaluable Analysis Set (EAS) is a subset of the FAS and includes all participants treated with at least one dose of capmatinib monotherapy, who have measurable disease at baseline, and centrally confirmed MET amplification. This analysis set will be used for the primary efficacy endpoint and the analysis of the secondary efficacy endpoints at the interim and primary analysis.

10.2.3 Combination Analysis Set

The Combination Analysis Set (Combo Analysis Set, CAS) is a subset of the FAS and includes all participants who are treated with capmatinib monotherapy, receive at least one dose of the capmatinib + nazartinib combination therapy, have a baseline tumor assessment prior to the start of the combination treatment dosing, and have centrally confirmed MET amplification. In case both stages of the study are completed, this analysis set will be used for the analysis of the efficacy of the capmatinib plus nazartinib combination therapy for Group 5.

10.2.4 Safety Set

The Safety Set includes all participants who received at least one dose of study treatment (capmatinib monotherapy or capmatinib + nazartinib combination therapy).

10.3 Participant demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively by treatment group for the FAS.

10.4 Treatments (study treatment, concomitant therapies, compliance)

Duration of exposure to study treatment in days, as well as actual total doses, actual dose intensities, and relative dose intensities of both study drugs will be summarized using descriptive statistics by treatment group for the safety set.

Compliance to the study treatment will be assessed by the number of dose reductions, number of dose interruptions and percent of days received planned dose for both study drugs separately in summary tables by treatment group for the safety set.

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

10.5 Primary objective for Phase Ib and Phase II Groups 1 to 4

Phase Ib: To estimate the MTD or RP2D of nazartinib in combination with capmatinib in $EGFR^{L858R/ex19del}$ NSCLC participants who have progressed on EGFR TKI treatment (e.g. gefitinib, erlotinib or afatinib).

Phase II: To estimate the preliminary anti-tumor activity of nazartinib in combination with capmatinib measured by overall response rate (ORR) determined by the Investigators' assessment in accordance with RECIST 1.1 in each of the Groups 1 to 3. To characterize the safety and tolerability of nazartinib in combination with capmatinib taken with food in Group 4.

Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant): at least 40 NSCLC participants with EGFR activating mutation (L858R or ex19del or other rare mutations such as L861Q, G719X and S768I) who had disease progression on one and only one prior treatment with a first or second generation EGFR TKI. The enrollment will continue until 20 participants with an acquired EGFR T790M+ mutation (subgroups 1a + 1c) and 20 participants without the T790M mutation (subgroups 1b + 1d) have entered the treatment phase. The resistance mechanism status will be determined centrally by the Novartis designated laboratory and prospectively tracked in the IRT system.

Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve): approximately 5 NSCLC participants who are EGFR inhibitor treatment naïve and harbor T790M de novo mutation.

Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic): at least 40 treatment naïve NSCLC participants with EGFR activating mutation (L858R or ex19del) and no T790M mutation, nor MET dysregulation. The resistance mechanism status will be determined centrally by the Novartis designated laboratory and prospectively tracked in the IRT system.

Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic): approximately 30 NSCLC participants with EGFR activating mutation (e.g.: L858R or ex19del) who failed (defined as intolerance to treatment or documented disease progression) on maximum 2 prior lines of antineoplastic therapies in the advanced setting. The resistance mechanism status will be determined centrally by the Novartis designated laboratory and prospectively tracked in the IRT system. Group 4 participants will take study drug with food (unrestricted meal type).

For the purpose of this study, common EGFR activating/sensitizing mutations are L858R point mutation and exon 19 deletions which account for approximately 90% of the cases. Other rare EGFR mutations such as L861Q, G719X, and S768I are also considered activating/sensitizing mutations for enrollment onto the Phase II Group 1, Group 3 and Group 4.

10.5.1 Variable

Phase Ib: Incidence of dose limiting toxicities (DLTs) in Cycle 1. Estimation of the MTD of the study treatment will be based upon the estimation of the probability of DLT in Cycle 1 for

participants in the DDS. This probability is estimated by the model described in Section 10.4.2.

Phase II, Group 1–3: Overall response rate, determined as the proportion of participants experiencing a best overall response of confirmed CR or PR per RECIST 1.1 at any time on study by investigator assessment.

ORR will be estimated by group and for Group 1 by T790M status as assigned based on baseline mutation status and prior systemic antineoplastic therapy.

Phase II, Group 4: Frequencies of treatment-emergent adverse events.

10.5.2 Statistical hypothesis, model, and method of analysis

10.5.2.1 Phase Ib

An adaptive BLRM guided by the EWOC principle will give recommendations to the dose escalation of the proposed combination treatment to its MTD/RP2D. The DLT data in DDS from the first cycle of treatment accumulated throughout the dose escalation part will be used for modeling the dose-DLT relationship of nazartinib when given in combination with capmatinib.

The BLRM is formulated as follows: let $\pi_1(d_1)$ be the probability of a DLT if nazartinib is given as a single agent (q.d. schedule) at dose d_1, and $\pi_2(d_2)$ the probability of a DLT if capmatinib is given as a single agent (b.i.d.) at dose d_2.

The marginal dose-DLT relationships are then modeled as:

nazartinib: $\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

capmatinib: $\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$,

where $\text{logit}(\pi.(d.)) = \log[\pi.(d.)/\{1 - \pi.(d.)\}]$, nazartinib reference dose $d_1^* = 300$ mg (q.d.) and capmatinib reference dose $d_2^* = 200$ mg (b.i.d., so total daily dose 400 mg), and $\alpha_1, \alpha_2, \beta_1, \beta_2 > 0$.

The combination dose-response relationship is subsequently modeled as:

$$\text{Odds}(\pi_{12}(d_1,d_2)) = \pi_{12}(d_1,d_2)/(1 - \pi_{12}(d_1,d_2))$$

$$= \exp(\eta(d_1/d_1^*)(d_2/d_2^*))(\pi_1(d_1) + \pi_2(d_2) - \pi_1(d_1)\pi_2(d_2))/((1 - \pi_1(d_1))(1 - \pi_2(d_2))),$$

where the interaction term $-\infty < \eta < \infty$ is a scalar.

The Bayesian approach requires the specification of prior distributions for the model parameters. The prior distributions and the process for their derivation and update based on available pre-clinical and clinical data are provided in Section 14.2, along with examples of hypothetical decisions that may be followed during the dose escalation.

Starting dose combination using the tablet formulation of nazartinib

Once the tablet formulation of nazartinib is ready to be used in the new cohort, (i) data from all the previous cohorts of this study and (ii) updated DLT data from the three single agent studies [redacted] and [CEGF816X2101] will be appropriately down-weighted (refer to Appendix 2 for more details on down-weighting data coming from different

sources) and used to run the BLRM. Results from the BLRM with EWOC principle will be used to support the starting dose for the new formulation as mentioned in Section 6.2.1.

The starting dose for each of the components of the combination cannot be higher than those already used in the previous cohorts for the same dose escalation.

Dose recommendation

Dose recommendation will be based on summaries of the posterior distribution of model parameters and the posterior distribution of DLT rates, including the mean, median, standard deviation, 95% credibility interval, and the probability that the true DLT rate for each dose combination lies in one of the following categories:

- [0%, 16%) under-dosing
- [16%, 35%) targeted toxicity
- [35%, 100%] excessive toxicity

Following the principle of EWOC, after each cohort of participants the recommended dose combination is the one with the highest posterior probability of DLT in the target interval [16%, 35%) among the doses fulfilling the overdose criterion that there is less than 25% chance of excessive toxicity. Decisions on dose escalation will follow the procedure outlined in Section 6.2.3.

Listing/ summary of DLTs

DLTs will be listed and their incidence summarized by primary system organ class, preferred term and by treatment group. The dose-determining set will be used for these summaries.

10.5.2.2 Phase II

A simple Bayesian design will be used in order to estimate the ORR and to provide inferential summaries (e.g., mean, median, standard deviation, 95% credible intervals, and interval probabilities) based on the posterior distribution of ORR in the Phase II part. Minimally informative unimodal Beta distributions (Neuenschwander et al 2008) will be used as prior distribution for the different study groups. These prior distributions reflect the current uncertainty about the efficacy of capmatinib in combination with nazartinib. For the primary analysis the posterior distributions of the ORR will be computed using the available data.

The primary analysis will be performed using the FAS when all participants enrolled in each of the Groups 1 to 4 have completed at least 6 cycles of treatment or discontinued prior to that time for any reason.

Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic) will have one interim analysis for futility when approximately 20 participants have completed at least 4 cycles of treatment or discontinued treatment prior to that time.

Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant)

For participants harboring the T790M mutation and participants not harboring the T790M mutation the posterior distribution of the ORR will be computed using the available data at the time of the primary analysis. A minimally informative beta distribution with parameters

a = 0.1765 and b = 1 based on a conservative assumption about the mean response rate will be used.

Summaries (e.g., mean, median, standard deviation, 95% credible intervals, and interval probabilities) for the posterior distribution of the ORR will be provided for the T790M+ and T790M− subgroup.

Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve)

This group will only be analyzed descriptively due to the expected maximum number of 5 participants enrolled.

Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic)

The ORR will be classified according to the following intervals:

- [0, 40%) unacceptable anti-tumor activity
- [40%, 55%) limited anti-tumor activity
- [55%, 70%) moderate anti-tumor activity
- [70%, 100%] strong anti-tumor activity

An observed ORR ≥ 55% based on Investigators' assessments will be considered clinically meaningful in this group.

The preliminary anti-tumor activity of the study treatment will be declared if the following two conditions are both fulfilled:

- The posterior median ORR is equal to or greater than 55%
- The posterior risk of being in the unacceptable anti-tumor activity interval is lower than 5%

This will require observing at least 22 responses in 40 participants. Otherwise, the inferential summaries for the 4 intervals above will be assessed for further characterization of the anti-tumor activity. A minimally informative beta distribution with parameters a = 1 and b = (1 – 0.55)/0.55 = 0.818 based on an assumed mean response rate of 0.55 will be used as prior distribution for the Bayesian estimation of the ORR.

An interim analysis for futility will be performed when approximately 20 participants have completed at least 4 cycles of treatment or discontinued treatment prior to that time. More details on the interim analysis are presented in nazartinib.

Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic)

Frequencies of adverse events will be analyzed descriptively in this group as described in Section 10.6.1.2.

10.5.3 Handling of missing values/censoring/discontinuations

Incidence of DLTs in Cycle 1: If a Phase Ib participant is considered as non-evaluable for the DDS, enrollment of a new participant to the current cohort will be considered if there is less than the required number of evaluable participants (Section 6.2.3).

Overall response rate: Participants who have missing BOR will be considered as a treatment failure for the primary analysis of ORR.

Participants who have disease progression and continue to receive study drug after progression will qualify for PD at the time of progression and will be counted as PD in the derivation of efficacy endpoints.

10.5.4 Supportive analyses

For the Phase II part the Bayesian analysis of ORR for each Group will be repeated using the PPS, if the PPS is different from the FAS.

[redacted]

10.6 Primary objective for Phase II Group 5

Approximately 30 participants will be enrolled in Group 5.

Group 5 will have one interim analysis for futility when 10 participants have completed at least 2 tumor assessments while on treatment with capmatinib monotherapy, had radiological disease progression per RECIST 1.1, or discontinued study treatment prior to that time. Details on the interim analysis are presented in Section 10.8.

10.6.1 Primary estimand

The primary scientific question of interest is to estimate the treatment effect of capmatinib monotherapy based on ORR for the target population regardless of discontinuation of treatment and any unforeseen events resulting from a public health emergency.

Targeting this treatment effect is regarded as a measure for the contribution of capmatinib monotherapy in this population setting within a novel drug combination (capmatinib + third generation EGFR TKI Inhibitor). It is indicated that the median time to response for capmatinib is approximately 6 weeks (Wolf et al 2020). Moreover, a capmatininb monotherapy period will allow a thorough toxicity washout of the previous TKI. It is reported that a medium washout period for switching of TKIs of 1.1 months (Sakata et al. 2020).

The primary estimand is characterized by the following attributes:

1. Population: adult NSCLC participants with previously documented EGFR activating mutation (e.g., L858R and/or ex19del), T790M negative, MET amplified (confirmed by central testing), who have progressed on one prior line of therapy (either to first/second generation EGFR TKIs, osimertinib or other third generation EGFR TKIs) for advanced/metastatic disease NSCLC. Further details on the population are provided in Section 5.
2. Treatment: capmatinib monotherapy at a dose of 400 mg b.i.d. (tablets for oral use). Further details about the treatment are provided in Section 6.1.
3. Variable: BOR defined as the best response recorded from the date of treatment start until radiological disease progression/recurrence (taking as reference for disease progression the smallest measurements recorded since the treatment started) based on investigator assessment per RECIST 1.1 with responses after switching to capmatinib plus nazartinib

combination treatment and responses after the use of new (non-study treatment) anti-cancer therapy considered as non-response.

4. Intercurrent events:
   - Switching to capmatinib plus nazartinib combination treatment: BOR assessments after switching will be considered as nonresponses and have been accounted for in the variable attribute using the composite strategy
   - Start of new anti-cancer therapy: BOR assessments after the use of new anti-cancer therapy will be considered as nonresponses and have been accounted for in the variable attribute using the composite strategy
   - Discontinuation of study treatment for any reason (other than starting combination treatment or new anti-cancer therapy): BOR will take into account all response assessments irrespective of the reasons for discontinuing capmatinib monotherapy (treatment policy strategy)
   - Any unforeseen intercurrent events (e.g., related to a public health emergency) will be handled by the treatment policy strategy
5. Summary measure: ORR defined as the proportion of participants with confirmed BOR of CR or PR based on investigator assessment per RECIST 1.1

10.6.2 Statistical model, hypothesis, and method of analysis

The analysis of the primary endpoint will be performed for participants in the EAS who were treated with capmatinib monotherapy and based on the time period of monotherapy treatment. ORR is defined as the proportion of participants with confirmed best overall response of CR or PR, and will be assessed by the investigator according to RECIST 1.1.

The analysis of Group 5 data will be performed when all participants enrolled in the group have completed at least 6 treatment cycles (about 6 months) or discontinued prior to that time for any reason, provided the Group 5 continued into Stage 2.

The primary efficacy endpoint ORR will be estimated and the 2-sided exact 95% CI (Clopper and Pearson 1934) provided. Capmatinib monotherapy treatment will be considered to have clinically relevant efficacy if the following criteria are fulfilled:

- the ORR estimate is > 45% and
- the lower bound of the two-sided 95% exact CI is >35%.

Based on historical data (Soria et al 2015, Mok et al 2017), the ORR in this population is expected to be around 35% and the threshold of 45% is considered of clinical interest.

10.6.3 Handling of intercurrent events of the primary estimand

The intercurrent events for the primary estimand are described in Section 10.5.1.

10.6.4 Handling of missing values not related to intercurrent events

Participants without a baseline tumor assessment will not be included in the EAS.

10.7 Secondary objectives

10.7.1 Safety objectives

10.7.1.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used if not otherwise specified. All listings and tables will be presented by treatment group.

Phase Ib and Phase II Group 1 to Group 4

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

- pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
- on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- post-treatment period: starting at day 31 after last dose of study medication.

Phase II Group 5

For the safety analysis of capmatinib monotherapy in Group 5, the overall observation period will be divided into the following three mutually exclusive segments:

- pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
- on-treatment period:
  - from day of first dose of study medication to 30 days after last dose of capmatinib monotherapy, if the participant did not continue on combination therapy, or
  - from day of first dose of study medication to the data prior to the start of capmatinib plus nazartinib combination therapy, if the participant continued on combination therapy
- post-treatment period:
  - starting at day 31 after last dose of study medication, i.e., capmatinib monotherapy, if the participant did not continue on combination therapy, or
  - starting at day 31 after last dose of combination therapy, if the participant received combination therapy.

For the safety analysis of capmatinib plus nazartinib combination therapy 5, the overall observation period will be divided into the following three mutually exclusive segments:

- pre-treatment period: from day of participant's informed consent to the day before the first dose of combination therapy
- on-treatment period: from day of first dose of combination therapy to 30 days after last dose of study medication
- post-treatment period: starting at day 31 after last dose of study medication.

10.7.1.2 Adverse events (AEs)

Summary tables for AEs have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged. Listings of all AEs will be provided based on the FAS.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class or preferred term, severity (based on CTCAE grades), relationship to study treatment and by treatment group.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by participant and tabulated by type of adverse event and treatment group.

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

10.7.1.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03 for participants in Phase Ib and Phase II (Groups 1 to 4) and version 5.0 for participants in Phase II Group 5, the study's biostatistical and reporting team will grade laboratory data accordingly. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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

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

- frequency table for newly occurring on-treatment grades 3 or 4 (see below for details)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

10.7.1.4 Other safety data

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all participants with at least one abnormality.

Vital signs

- shift table baseline to worst on-treatment result

- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.7.1.5 Tolerability

Tolerability of study drugs will be assessed by summarizing the frequency of dose interruption, frequency of dose reduction, and dose intensity. Reasons for dose interruption and dose reduction will be listed by participant and summarized.

10.7.2 Efficacy objectives

CT/MRI assessments will be used for all efficacy assessments of anti-tumor activity on study. BOR, ORR, PFS, DCR, duration of response (DOR) and Time To Response (TTR) will be defined as per RECIST 1.1 (see Section 14.1) based on investigator assessment. The analyses will be based on the FAS for groups 1 to 4 and the EAS for Group 5. Summaries by group will be based on baseline mutation status and prior systemic antineoplastic therapies as specified in the eCRF. Listings of efficacy endpoints will be presented by treatment group.

If available, the results of the central evaluations by BIRC may be used for secondary analyses purposes.

10.7.2.1 Secondary efficacy endpoints for Phase Ib and Phase II Groups 1 to 4

Phase Ib part: Overall response rate (ORR), duration of response (DOR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) by Investigator assessment in accordance with RECIST 1.1 and overall survival (OS).

Phase II part: DOR, DCR, TTR, PFS by Investigator assessment in accordance with RECIST 1.1, and overall survival (OS). In addition for Group 4 ORR by investigator assessment in accordance with RECIST 1.1.

Best overall response

BOR is the best response recorded from the start of the treatment until documented radiological disease progression/recurrence. However, any assessments taken more than 28 days after the last dose of study treatment will not be included in the best overall response derivation.

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

BOR will be summarized by treatment group.

Overall response rate

ORR is defined as the proportion of participants with a best overall confirmed CR or PR per RECIST 1.1.

ORR will be estimated together with the exact binomial 95% confidence interval (CI) (Clopper and Pearson 1934).

Duration of response

Among participants with a confirmed PR or CR per RECIST 1.1, DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to underlying cancer. If a participant did not have an event or received any further anticancer therapy before documented disease progression, DOR is censored at the time of the last adequate tumor assessment.

DOR will be described using the Kaplan-Meier method including the estimated median (in months) with 95% CI, as well as the 25th and 75th percentiles. For the Phase Ib part the summary will be provided only in treatment groups with sufficient numbers of participants. Summary statistics of DOR for participants whose best response is CR or PR will be provided for groups with ≤ 5 responders. For the Phase II part a Kaplan Meier plot will also be presented.

Disease control rate

DCR is defined as the proportion of participants with BOR of CR, PR, or stable disease (SD) per RECIST 1.1.

DCR will be estimated by treatment group and for the Phase II part by T790M status in Group 1 and by sub-group otherwise together with the exact binomial 95% CI (Clopper and Pearson 1934).

Time to response

TTR is defined as the time between the date of start of treatment and the date of first documented response (CR or PR, which must be confirmed subsequently). For participants who did not achieve a confirmed PR or CR, the TTR will be censored at the last adequate tumor assessment date.

TTR will be described using the Kaplan-Meier method including the estimated median (in months) with 95% CI, as well as the 25th and 75th percentiles. For the Phase Ib part the summary will be provided only in treatment groups with sufficient numbers of participants. Summary statistics of TTR for participants whose best response is CR or PR will also be provided.

Progression-free survival

PFS is defined as the time from the date of first dose of study treatment to the date of first documented disease progression per RECIST 1.1 or death due to any cause. If a participant did not have an event or received any further anticancer therapy before documented disease progression, PFS will be censored at the time of the last adequate tumor assessment. By default, if disease progression or death is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression or death is documented after two or more missing tumor evaluations, the PFS time of these participants will be censored at the date of the last adequate tumor assessment without PD. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression.

PFS will be described using the Kaplan-Meier method including the estimated median (in months) with 95% CI, 25th and 75th percentiles. For the Phase Ib part the summary will be

provided only in treatment groups with sufficient numbers of participants. For the Phase II part a Kaplan Meier plot will also be presented. In addition, the PFS rates and 95% confidence intervals at 6, 12, 18 and 24 months will be estimated.

Overall survival

OS is defined as the time from the date of first dose of study treatment to the date of death due to any cause. Overall survival time for participants who are alive at the analysis cut-off date, who withdrew consent, or are lost to follow-up will be censored at the date of last contact prior to the cut-off date.

OS will be described using the Kaplan-Meier method including the estimated median (in months) with 95% CI, 25th and 75th percentiles, as well as the corresponding plot. The summary will be provided only in treatment groups with sufficient numbers of participants.

10.7.2.2 Secondary efficacy endpoints for Phase II Group 5

DOR, DCR, and PFS for capmatinib monotherapy will be analyzed as secondary efficacy endpoints for Group 5.

The analyses will be based on the EAS. The endpoint definition follows the description in Section 10.6.2.1.

10.7.3 Pharmacokinetics

The PAS will be used in all concentration pharmacokinetic data analysis and PK concentration summary statistics. The FPAS will be used for all PK parameters summary statistics.

For each of the three analytes capmatinib, nazartinib and LMI258, concentration data will be listed and summarized by Cycle, Study Day, time point, and treatment group (i.e. each dose combination of capmatinib and nazartinib in the Phase Ib part and Group 1, 2, 3 or 4 in the Phase II part, respectively). Descriptive statistics will include arithmetic and geometric mean, median, standard deviation, coefficient of variation (CV%), geometric mean CV%, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Individual concentration-time profile as well as mean concentration-time profile will be plotted.

PK parameters will be determined for all PK-evaluable participants with non-compartmental method(s) using Phoenix WinNonlin version 6.2 or above (Pharsight, Mountain View, CA). [redacted] Derived PK parameters, such as those listed in Table 10-1, will be summarized with descriptive statistics, including arithmetic and geometric means, median, standard deviation, CV%, geometric mean CV%, minimum and maximum. Only median values and ranges will be given for Tmax. Missing data will not be imputed.

To estimate the effect of food on the PK of capmatinib and nazartinib when given in combination with food after a single dose at steady state, the PK data on Cycle 1 Day 1 and on Cycle 2 Day 1 from Phase II Group 4 will be compared to the PK data with fasted condition from Phase Ib, and other Groups of Phase II.

The primary PK parameters (AUC0-t and Cmax) on Cycle 1 Day 1 and on Cycle 2 Day 1 respectively, will be log-transformed and analyzed with an ANOVA model including food

status (fed or fasted) as fixed effect. The model-based, between-treatment mean differences and corresponding two-sided 90% confidence intervals (CIs) will be calculated on the log-scale. The between-treatment differences and 90% CIs will then be back transformed to the original scale to obtain the geometric mean ratios and corresponding 90% CIs. For Tmax, median and range of difference between treatment groups will be provided.

[redacted]

Table 10-1 Noncompartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (h*ng/ml^{-1})
AUC0-t	The AUC from time zero to t hours after administration (h*ng/ml)
AUCtau	The AUC calculated to the end of a dosing interval (tau) (h*ng/ml)
Cmax	The maximum (peak) observed plasma drug concentration after single dose administration (ng/ml)
Tmax	The time to reach maximum (peak) plasma drug concentration after single dose administration (h)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time^{-1}) may also be used for terminal elimination rate constant (time^{-1})
T1/2	The elimination half-life associated with the terminal slope (□z) of a semi logarithmic concentration-time curve (h). Use qualifier for other half-lives
CL/F	The total body clearance of drug from the plasma (L/h)
Vz/F	The apparent volume of distribution during terminal phase (associated with □z) (L)
Racc	The accumulation ratio, calculated as AUCtau/AUCtau(C1D1)

10.7.3.1 Data handling principles

Missing concentration values will be reported as is in data listings. Concentration values of capmatinib, nazartinib, and LMI258 below the respective Lower Limit of Quantitation (LLOQ, BLLOQ) will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

[redacted]

10.9 Interim analysis

Phase Ib part

No formal interim analyses are planned. However, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose-escalation part, the next dose will be chosen depending on the observed

data. Details of this procedure and the process for communication with investigators are provided in Section 6.2.3.

Phase II part

A futility interim analysis (IA) will be conducted for Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic) and Group 5 (EGFRmut, T790M-, MET GCN ≥ 5, 2L, EGFR TKI resistant). No interim analysis is planned for Groups 1, 2 and 4. However, individual participant data will be reviewed on an ongoing basis by the study team across the duration of the trial (Section 8.5).

Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic)

One interim analysis for futility will be performed for participants enrolled in Group 3 (participants in first line setting) when approximately 20 participants have completed at least 4 cycles of treatment or discontinued treatment prior that time. A close monitoring of the first 20 measurable participants will be performed. All evaluable participants at the time of the data cut-off for the interim analysis will be used.

The decision whether to continue or stop enrollment and/or treatment will be based on the probability of success (PoS). PoS is the probability to have a positive conclusion at the end of the study, given the interim data. Denoting the number of participants at interim by n_I and the number of responders at interim by r_I, PoS is found as

- PoS = Prob [at least $x-r_I$ responders in $40-n_I$ participants | r_I responders in n_I participants]

The number of responders ($x-r_I$) to be observed in the remaining $40-n_I$ participants follows a Beta-binomial distribution. This is used in order to calculate PoS.

The enrollment and/or treatment may be stopped at the interim analysis if PoS<0.10, i.e., if less than 9 out of the first 20 participants have the best response of CR or PR. The criterion (number of responders) will be based on the actual number of participants in the FAS at the time of the interim analysis.

If futility is concluded, the enrollment of 1L participants (Group 3 and 1L participants in Group 4) may be stopped. The enrollment in opened groups with pre-treated participants will continue.

Table 10-2 provides the probabilities of success at the primary analysis based on different numbers of responders observed at the interim analysis. For 9 or more responders PoS exceeds 0.10 and the study will continue at interim.

Table 10-2 Probability of success at the primary analysis based on various numbers of responders observed at the IA for Group 3

Responders at IA out of 20 evaluable participants at IA	Probability of Success
8/20	0.04
9/20	**0.14**
10/20	0.33
11/20	0.57
12/20	0.79

Group 5 (EGFRmut, T790M-, MET GCN ≥ 5, 2L, EGFR TKI resistant)

An interim analysis for futility will be performed based on stage 1 of the 2-stage design of Group 5 when 10 participants have completed at least 2 tumor assessments while on treatment with capmatinib monotherapy, had radiological disease progression per RECIST 1.1, or discontinued capmatinib monotherapy treatment prior that time. Recruitment will be on temporary halt while conducting the IA. The IA will be based on the EAS.

The decision to stop for futility at the interim analysis will be based on the predictive probability (PP) that the final observed ORR of capmatinib monotherapy is no worse than the historical control ORR, given the interim observed data (x) and responders among n participants. Based on available data (Soria et al 2015, Mok et al 2017), the ORR in the historical control for this population is expected to be around 35%. Thus, the stop for futility rule is based on

PP = Prob[Final observed ORR of capmatinib monotherapy ≥ 35% | x, n]

A minimally informative Beta distribution prior with prior mean equal to 35% will be used, i.e., the prior distribution will be Beta (0.5385, 1) for the futility stopping decision rule calculations at the interim analysis.

The group will be stopped for futility at the interim analysis if the PP <1%, i.e., if 0 response out of the first evaluable 10 participants is observed. For the purpose of the interim analysis a responder is defined as participant having a response of PR or CR per RECIST 1.1.

All evaluable participants at the time of the data cut-off for the interim analysis will be used to obtain the futility boundary using the stopping criteria. The futility boundary will be calculated according to the actual number of evaluable participants (in the EAS) in the interim analysis.

Table 10-3 presents the PP at the final analysis based on different numbers of responders observed at the interim analysis and an observed ORR of not worse than 0.35 for capmatinib monotherapy.

Table 10-3 Predictive probability (PP) for ORR of capmatinib monotherapy at the final analysis based on various numbers of responders observed at the IA for Group 5

Responders at IA out of 10 evaluable participants at IA	Predictive probability (PP)
0	0.0000
1	0.0148
2	0.0984
3	0.3207
4	0.6301
5	0.8686
6	0.9720
7	0.9967
8	0.9998
9	1.0000
10	1.0000

With 10 evaluable participants for the interim analysis, if no (0) response is observed (PP <1%), the Group 5 will be stopped for futility.

10.10 Sample size calculation

Phase Ib part

Cohorts of 3 to 6 evaluable participants will be enrolled in the dose-escalation part including at least six participants at the MTD/RP2D level, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 participants may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and pharmacokinetic parameters as required. At least 18 participants are expected to be treated in the dose escalation part, for the model to have reasonable operating characteristics relating to its MTD recommendation.

Phase II part

Approximately 145 participants (40 in Group 1, 5 in Group 2, 40 in Group 3, 30 in Group 4 and 30 in Group 5) will be enrolled in the study if Group 3 or Group 5 is not stopped for futility at the time of the interim analysis.

Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant)

As specified in Section 4.1, the number of participants harboring the T790M mutation among sub-groups 1a and 1c is minimum 20, for participants who do not harbor the T790M mutation among sub-groups 1b and 1d it is also minimum 20. The actual total sample size in Group 1 may be greater than 40.

Table 10-4 shows the 95% credible intervals based on the posterior distribution for different observed number of responses. The highlighted rows show examples that might be observed for the T790M+ or T790M− participants. If 5 responses out of 20 participants are observed, there is 95% probability that the ORR is between 9.1% and 44.3%, whereas it is between 32.0% and 73.1% when 11 responses are observed. To have at least 97.5% probability that the ORR is larger than 50%, 15 or more responses are required.

Table 10-4 Credible intervals for assumed observed responses in Group 1

Sample Size	Observed responses	Median	95% Credible Interval
20	4	0.188	[0.062, 0.386]
20	**5**	**0.236**	**[0.091, 0.443]**
20	6	0.285	[0.124, 0.497]
20	10	0.480	[0.277, 0.688]
20	**11**	**0.529**	**[0.320, 0.731]**
20	12	0.577	[0.365, 0.772]
20	15	0.724	[0.512, 0.882]

Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve)

The sample size for this group is based on the potential number of participants with the rare condition who can be enrolled into the study and not on formal sample size or operating characteristic calculations.

Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic)

The operating characteristics of the statistical design are presented below with the probabilities to stop for futility at the interim analysis and to declare preliminary anti-tumor activity of the study treatment at the primary analysis (observing at least 22 responses in 40 participants) under different true ORR values (see also Table 10-5).

The actual total sample size in Group 3 may be greater than 40.

- If the true ORR is 40%, it is likely to stop at the interim analysis (probability 0.596) and the probability to declare preliminary anti-tumor activity at the end of the study is low (0.038).
- If the true ORR is 55%, the probability to stop at the interim analysis is low, 0.131, and the probability to declare preliminary anti-tumor activity at the end of the study is 0.553.
- If the true ORR is 70%, it is highly unlikely that the study would be stopped at the interim analysis (probability 0.005) and the probability to declare preliminary anti-tumor activity at the end of the study is very high (0.982).

Table 10-5 Operating characteristics for ORR in Group 3

True ORR	Probability to stop for futility at IA	Success probability at primary analysis
0.40	0.596	0.038
0.45	0.414	0.129
0.50	0.252	0.309
0.55	**0.131**	**0.553**
0.60	0.057	0.780
0.65	0.020	0.923
0.70	0.005	0.982
0.75	0.001	0.998
0.80	0.000	1.000

Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) 2-3L antineoplastic)

The size of this group is based on practical considerations, not on formal sample size or operating characteristic calculations. The precision of estimates in the PK analysis which can be expected with the planned sample size of 20 participants with full PK blood samples is detailed below.

Based on published data (Tan et al 2017) at the RP2D (capmatinib 400 mg b.i.d. + 100 mg q.d. nazartinib) based on the Phase Ib data, the CV% of Cmax and AUC0-12 for v would be at most 49.4% and 48.3%, and the CV% of Cmax and AUC0-24 for nazartinib would be at most 58.9% and 78.7%. To be conservative, the CV% of 49.4% for capmatinib PK and 78.7% for nazartinib PK was used in the calculation below.

When combining fasted PK data from Phase Ib (n=10) at the RP2D and fasted PK from Group 1 (approximately n=3) and from Group 3 (n=10) in Phase II, a total of about n=23 participants would have full PK in the fasted state. In Group 4 in Phase II, n=20 participants may have full PK in the fed state.

With such sample size (n=23 in the fasted status, and n=20 in the fed status), the half-width of a 90% CI on the log-scale is 0.239 and 0.355 from the observed mean difference of log (PK) for capmatinib and nazartinib, respectively. Once transformed back to the original scale, this

translates into the 90% CI shown in Table 10-6, under different assumptions of what the true ratio of the PK parameters is.

Table 10-6 Expected 90% confidence limits for different ratios of geometric means

	Capmatinib PK		nazartinib PK	
True ratio	Lower Limit of 90% CI	Upper Limit of 90% CI	Lower Limit of 90% CI	Upper Limit of 90% CI
0.70	0.550	0.890	0.490	1.001
0.80	0.629	1.107	0.560	1.143
1.00	0.786	1.272	0.700	1.429
1.25	0.983	1.590	0.875	1.787
1.50	1.179	1.908	1.049	2.144
2.00	1.573	2.544	1.399	2.859
2.50	1.966	3.179	1.749	3.573

Group 5 (EGFRmut, T790M-, MET GCN ≥ 5, 2L, EGFR TKI resistant)

The operating characteristics (with 30 participants and assuming an interim analysis after Stage 1 at 10 participants) were determined for the primary objective to estimate the treatment effect of capmatinib monotherapy. Based on available data (Soria et al 2015, Moket al 2017), the ORR in the historical control for this population is expected to be around 35%. The success criterion defined in Section 10.5.2 requires an estimated ORR of >45% and a lower bound of the two-sided 95% exact CI of >35% to conclude that the antitumor activity is of clinical interest.

Table 10-7 presents the probability of stopping at the interim analysis, the probability for a positive conclusion (i.e., not stopped at IA for futility and success criteria met at final analysis after stage 2) and for a negative conclusion (i.e., not stopped at IA for futility but success criteria not met at final analysis) under different underlying true ORR of capmatinib monotherapy.

The operating characteristics have up to around 35% probability of stopping the trial for futility when the true ORR is ≤ 35%. Also, when the true ORR is 45% then the probability of positive conclusion at the final analysis with 30 participants is ca. 50%. If the true ORR is 50% or higher, the probability of a positive conclusion at the final analysis with 30 participants is >70%.

To adjust for potential discordance between local vs central MET amplification testing results, additional participants may be enrolled to ensure there are at least 10 in stage 1 and 30 in total MET amplified participants centrally confirmed by Novartis-designated laboratory.

Table 10-7 Operating characteristics for various assumed true ORR of capmatinib monotherapy

True ORR	Probability to stop at IA* (%)	Probability of positive conclusion at final analysis (%)	Probability of negative conclusion at final analysis
0.10	34.87	0.00	65.13
0.20	10.74	0.09	89.17
0.25	5.63	0.82	93.55
0.30	2.82	4.00	93.17
0.35	1.35	12.63	86.02

True ORR	Probability to stop at IA* (%)	Probability of positive conclusion at final analysis (%)	Probability of negative conclusion at final analysis
0.40	0.60	28.55	70.85
0.45	0.25	49.75	50.00
0.50	0.10	70.76	29.14
0.55	0.03	86.44	13.53
*Assuming interim analysis at 10 evaluable participants			

10.11 Power for analysis of key secondary variables

Not applicable

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECss and regulatory authorities as required.

11.3 Informed consent procedures

Eligible participants may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent if applicable, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the participant. In cases where the participant's representative gives consent, the participant should 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 should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the participant source documents. The date when a participant's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH E6 GCP guidelines and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

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

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

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

[redacted]

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database e.g. such as clinicaltrials.gov, before study start. In addition, results of interventional clinical trials in adult participants are posted on novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of upon study completion (i.e., LPLV), and finalization of the study report the results of this

study will be either submitted for publication and/or posted in those for interventional clinical trials involving pediatric participants within 6 months of study completion.

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

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

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

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

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For

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

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

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

11.7 Confidentiality of study documents and participant records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IECOnly amendments that are required for participant safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any 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 (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 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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Document status:	Version 3.2: 11-Feb-2016 Version 3.1: 29-Nov-2011 Version 3:0: 19-Oct-2009 Version 2:0: 18-Jan-2007 Version 1:0: 13-Dec-2002
Release date:	11-Feb-2016
Authors (Version 3.2)	[redacted]
Authors (Version 3.1):	
Authors (Version 3):	
Authors (Version 2):	
Authors (Version 1):	

Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
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

14.1.1 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 14.1.2 and the definition of best response in Section 14.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.3.2 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 14.1.4 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.

14.1.2 Efficacy assessments

14.1.2.1 Definitions

14.1.2.1.1 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 14.1.3.2.9.

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:**
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.1.2.1.2 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 14.1.3.2.9.

14.1.2.2 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However,

another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.

- **FDG-PET:** can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Physical exams: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 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 limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions

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

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

14.1.2.3 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 14.1.2.1.1.
- **Nodal target:** See Section 14.1.2.1.1.

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.

14.1.2.4 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 14-1) and non-target lesions (Table 14-2) identified at baseline. These

evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

14.1.2.4.1 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.

14.1.2.4.1.1 Non-nodal lesions

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

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

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

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

14.1.2.4.1.2 Nodal lesions

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

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

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

14.1.2.4.2 Determination of target lesion response

Table 14-1 Response criteria for target lesions

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

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

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

[3.] In exceptional circumstances an UNK response due to change in the method could be over-ruled by the investigator or central reviewer using expert judgement based on the available information (see notes on the target lesion response and methodology change See Section 14.1.2.2.

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 progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements:** In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is

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

- **Nodal lesion decrease to normal size:** When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split:** In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced:** Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
  - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
  - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
  - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
  - A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria

14.1.2.4.3 Determination of non-target lesion response

Table 14-2 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 review does prevail and the progression status should be confirmed later on by the review panel (or study chair). [2] It is recommended that the investigator and/or central reviewer should use expert judgement to assign a non-UNK response whether 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**' there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.1.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.2.2.

14.1.2.5 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 14-3.

Table 14-3 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 14.1.2.4.

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

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

14.1.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.3.2.9 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.3.1 Best overall response

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

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

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

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).

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

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 best overall response.

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

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

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

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

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

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

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. 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 best overall response 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 progressive disease within 8 weeks of the start of treatment.

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

14.1.3.2 Time to event variables

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

14.1.3.2.1 Progression-free survival

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

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

14.1.3.2.2 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.

14.1.3.2.3 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.

14.1.3.2.4 PFS2

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

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

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

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

14.1.3.2.5 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.

14.1.3.2.6 Duration of response

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

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

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

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

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

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

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

14.1.3.2.7 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 overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.3.2.6. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

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

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

Assessment date

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

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

Start dates

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

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

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.3.2.9).

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

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

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

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

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 14-4.

Table 14-4 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 14.1.2.4.		

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

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

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

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

14.1.3.2.10 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 SAP 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 14.1.3.2.8, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics-April 2005) as a reference, the following analyses can be considered:

Table 14-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) 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 (IIT 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 duration of response)

1. =Definitions can be found in Section 14.1.3.2.8.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.3.2.8.
3. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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

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

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

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

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

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

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

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

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

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 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 SAP documentation.

14.1.4 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).

14.1.4.1 Study/project specific decisions

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

14.1.4.2 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
- Subject/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

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

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

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

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

14.1.4.4 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 SAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

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

14.1.4.5 Programming rules

The following should be used for programming of efficacy results:

14.1.4.5.1 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.

14.1.4.5.2 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 14.1.3.2.8). If all measurement dates have no day recorded, the 1st of the month is used.

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

14.1.4.5.3 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.

14.1.4.5.4 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)'.

14.1.4.5.5 Study/project specific programming

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

14.1.4.5.6 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 duration of responses) the following censoring reasons are possible:
- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-5)

- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.1.3.2.8. 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.

14.1.5 References (available upon request)

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

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

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14.2 Appendix 2 - Prior derivation for the Bayesian logistic regression model and hypothetical dose escalation scenarios

An adaptive Bayesian Logistic Regression Model (BLRM) guided by the EWOC principle will give recommendations to the dose escalation of the proposed combination treatment to its MTD/RP2D. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2007) and by Rogatko (2007) and is one of the key elements of the FDA's Critical Path Initiative.

The BLRM will estimate the dose-DLT relationship of nazartinib when given in combination with capmatinib. This Bayesian analysis will be based on the DLT data (absence or presence of DLT) of the first 28 days of study treatment, accumulated throughout the Phase Ib dose-escalation part.

This section provides details about derivation of prior distributions for the model parameters, and the properties of the adaptive design in terms of dosing recommendations for hypothetical data scenarios and operating characteristics.

14.2.1 Statistical model

The BLRM is formulated as follows: let $\pi_1(d_1)$ be the probability of a DLT if nazartinib is given as a single agent at dose d_1 (q.d.), and $\pi_2(d_2)$ the probability of a DLT if capmatinib is given as a single agent at dose d_2 (b.i.d.).

The marginal dose-DLT relationships are then modeled as:

- nazartinib: $\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$
- capmatinib: $\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$,

where $\text{logit}(\pi.(d.)) = \log[\pi.(d.) / \{1- \pi.(d.)\}]$, nazartinib reference dose $d_1^* = 300$ mg (q.d.) and capmatinib reference dose $d_2^* = 200$ mg (b.i.d., so total daily dose 400 mg), and $\alpha_1, \alpha_2, \beta_1, \beta_2 > 0$.

The combination dose-DLT relationship is subsequently modeled as:

- $\text{Odds}(\pi_{12}(d_1,d_2)) = \pi_{12}(d_1,d_2)/(1- \pi_{12}(d_1,d_2))$
- $= \exp(\eta(d_1/d_1^*)(d_2/d_2^*))(\pi_1(d_1)+ \pi_2(d_2) - \pi_1(d_1)\pi_2(d_2))/((1- \pi_1(d_1))(1- \pi_2(d_2))$,

where the interaction term $-\infty < \eta < \infty$ is a scalar.

14.2.2 Methodology for data down-weighting

The cumulative dose-DLT information that has been generated from relevant studies/drug variants, called co-data, can be incorporated into the BLRM using a down-weighting method that considers between-trial/drug variant heterogeneity of data (Neuenschwander et al 2010). The weight "w" which will be given to each participant from one particular study and/or a drug variant is given by:

$$w = \frac{1}{1 + 2nr^2/\sigma^2} = \frac{1}{1 + 2n/n_{ess}}$$

where n is the sample size of this set of co-data, σ is the "outcome standard deviation" for one observation and τ is the between-trial/drug variant standard deviation. n^*_∞ is the maximum prior effective sample size under infinite historical information. σ will be chosen as 2. τ will be chosen depending on the degree of heterogeneity. For substantial heterogeneity, the maximum prior effective sample size is 16, which implies that τ is set to 0.5. For large heterogeneity, the maximum prior effective sample size is 4, which implies that τ is set to 1.

Note that there may be more than one study/drug variant from which we want to borrow information for the current study/drug variant. The weights will vary between these co-data sets depending on different sample sizes and also on different degrees of heterogeneity.

Table 14-6 shows the heterogeneity of data from different sources to be considered.

Table 14-6 Levels of heterogeneity for co-data from different studies and/or drug formulations

Co-data		**Levels of heterogeneity considered in data down-weighting**	
Study #	**Formulations**	**Formulation:** capmatinib **tablet + nazartinib capsule**	**Formulation:** capmatinib **tablet + nazartinib tablet**
[redacted]			
CEGF816X2101	nazartinib capsules	substantial	large
	nazartinib tablets	Large	substantial
[redacted]			

14.2.3 Prior specifications

The Bayesian approach requires the specification of prior distributions for the model parameters ($\log(\alpha_1)$, $\log(\beta_1)$) for nazartinib, ($\log(\alpha_2)$, $\log(\beta_2)$) for capmatinib and η for interaction. The derivation of the prior distributions is described below.

14.2.3.1 nazartinib prior specification for ($\log(\alpha_1)$, $\log(\beta_1)$)

Prior specification

A weakly informative bivariate normal prior for the model parameters ($\log(\alpha_1)$, $\log(\beta_1)$) as in the first-in-human study [CEGF816X2101] is taken as the prior for the nazartinib parameters.

Based on prior guesses (medians) from preclinical data and wide confidence intervals for the probabilities of DLT at each dose, the prior distribution is derived as follows:

- For the purposes of tuning the prior for the model, the median DLT rate at 75 mg q.d. is assumed to be at 0.1%, and the median DLT rate at 750 mg q.d. is assumed to be at 25%. For the remaining doses, median DLT rates a priori are assumed linear in the logit-scale as a function of log-dose.
- Based on the above specified medians for the DLT rate at certain doses and wide prior confidence intervals, the optimal parameters of the bivariate normal distribution can be obtained following the procedure described by Neuenschwander et al (2008).

The parameters of the derived prior distribution for ($\log(\alpha_1)$, $\log(\beta_1)$) are presented in Table 14-7.

Table 14-7 Prior distribution of model parameters ($\log(alpha_1)$, $\log(beta_1)$), as in CEGF816X2101

Parameter	Means	Standard deviations	Correlation
$\log(\alpha_1)$, $\log(\beta_1)$	-3.068, 0.564	2.706, 0.728	-0.817

Newly available dose-DLT data from the [CEGF816X2101] study will be used to update the model after down-weighting the data as mentioned in Section 14.2.1. Substantial heterogeneity will be assumed:

$$w_1 = \frac{1}{1 + 2n_1\tau_1^2/\sigma_1^2}$$

At the time of protocol amendment 1, new dose-DLT data has been available from study [CEGF816X2101] (refer to Table 14-9), and are included in the model to update the distribution of the DLT rate of the combination (as detailed in Section 14.2.3.4).

14.2.3.2 Capmatinib prior specification for ($\log(\alpha_2)$, $\log(\beta_2)$)

Historical data

The currently available dose-DLT data of capmatinib single agent in capsule formulation and b.i.d. dosing schedule from the following clinical studies are considered as the relevant information ([redacted]) and used to derive the prior distribution for the BLRM parameters ($\log(\alpha_2)$, $\log(\beta_2)$).

[redacted]

[redacted]

Prior specification

A mixture prior for the model parameters ($\log(\alpha_2)$, $\log(\beta_2)$), which are assumed to follow a bivariate normal distribution, is derived in the following steps as for [redacted]:

1. To use the historical dose-DLT data from the clinical studies in Table 14-8, each capsule dose level need to be converted to a tablet dose level. Given a conversion factor c, a capsule dose level d_c is considered to be equivalent to a tablet dose level $d_t = d_c/c$. Based on data of the relative bioavailability study [redacted] in healthy volunteers, the estimated relative exposure (AUC_{last}) of tablet vs. capsule has a geometric mean ratio of [redacted] and a 90% CI of [redacted]. To account for uncertainty of dose conversion between the two formulations, three values of c are considered: [redacted], i.e. the estimated mean and confidence limits, to generate three informative prior components (Table 14-9) using the meta-analysis predictive (MAP) approach:
   - The prior distribution of mean of ($\log(\alpha_2)$, $\log(\beta_2)$) is assumed to follow a normal distribution with mean [redacted] and standard deviation [redacted] for $\log(\alpha_2)$, and mean [redacted] and standard deviation [redacted] for $\log(\beta_2)$.
   - A substantial between-study heterogeneity is assumed and captured in the prior distributions of the standard deviations of ($\log(\alpha_2)$, $\log(\beta_2)$), denoted by τ_α and τ_β. Both τ_α and τ_β are assumed to follow a log-normal distribution with mean log([redacted]) and log([redacted]), respectively, and a standard deviation of [redacted] for both.
   - The prior distribution of correlation between $\log(\alpha_2)$ and $\log(\beta_2)$ is assumed to follow a uniform distribution in [-1, 1].

2. To take into account the potential, rare situation that the relative exposure estimated in healthy volunteers of [redacted] is not quite applicable to this study in NSCLC participants, a fourth prior component with weakly informative bivariate normal distribution is added to improve robustness of the final prior. The parameters of this weakly informative prior distribution are described below:
   - The mean of log(α_2) is set to logit([redacted]),where [redacted] is the posterior median of DLT rate of capmatinib capsule single agent at 500 mg (b.i.d.) (approximate to the tablet reference dose) based on the estimation provided to the most recent dose determining meeting of study [redacted]. The standard deviation of log(α_2) is set to [redacted].
   - The mean of log(β_2) is set to [redacted], assuming proportionality between dose and odds of DLT. The standard deviation of log(β_2) is set to [redacted].
   - The correlation between log(α_2) and log(β_2) is set to [redacted], assuming independence.
3. Finally, a mixture prior for (log(α_2), log(β_2)) is consisted of the four prior components generated in steps 1 and 2 above, with an equal weight to be allocated to the three informative prior components together and to the weakly informative component. Assuming the sampling distribution of the estimated geometric mean ratio specified in step 1 is approximately normal, the relative weights of the first three informative prior components with c values of [redacted] are determined by dividing the respective density values for the 50th, 5th and 95th percentiles of the standard normal distribution, i.e. [redacted]. The resulting relative weights for the three informative prior components are [redacted], corresponding to absolute weights of [redacted] for a total weight of [redacted]. The weakly informative prior component takes the remaining absolute weight of [redacted]

[redacted]

Newly available capmatinib dose-DLT data in tablet formulation from ongoing single agent studies, [redacted], will be used to update the model after down-weighting using the methodology mentioned in Section 14.2.1:

$$w_{2j} = \frac{1}{1 + 2n_{2j}\tau_{2j}^2/\sigma_{2j}^2}$$

At the time of protocol amendment 1, dose-DLT data of capmatinib tablet has been available from studies [redacted], and are included in the model to update the distribution of the DLT rate of the combination (as detailed in Section 14.2.3.4).

[redacted]

14.2.3.3 Interaction η

A non-informative prior reflecting the current uncertainty about the toxicity of the combination treatment is used for η. In order to allow for the potentiality of both synergy and antagonism of the safety profiles, it was assumed that η is normally distributed with median = 0 (no increase on odds of DLT, i.e. independence) and 97.5th percentile = log(10) (10-fold increase on odds of DLT). The mean and standard deviation of the prior distribution of η are 0 and 1.175, respectively.

14.2.3.4 Summary of the distribution of DLT rate

Currently available dose-DLT data from single-agent studies of [redacted] nazartinib (as of 9th Oct 2014) are summarized in Table 14-10 below.

Table 14-10 Available dose-DLT data from single-agent studies as of Oct. 2014

Agent	Study	Dose	# Participants	# DLT
[redacted]				
nazartinib (capsule)	CEGF816X2101	75 mg q.d.	7	0
		150 mg q.d.	3	0

Based on the parameter values specified in Table 14-7 [redacted] and in Section 14.2.3.3, and including the data in Table 14-10, the updated distribution of DLT rate at the provisional starting dose (nazartinib 50 mg q.d. and capmatinib 200 mg b.i.d.) is summarized in Table 14-11 below. The probability that the DLT rate is in the overdose interval [0.35, 1] is 0.005, satisfying the EWOC principle.

Table 14-11 Summary of DLT rate following incorporation of current dose-DLT data

	Probability that Pr(DLT) is in interval					Quantile		
nazartinib capsule dose and regimen	[0, 0.16)	[0.16, 0.35)	[0.35, 1]	Mean	Standard deviation	2.5%	50%	97.5%
capmatinib **200 mg** b.i.d.								
50 mg q.d.	0.914	0.081	0.005	0.069	0.064	0.002	0.051	0.238
100 mg q.d.	0.867	0.118	0.015	0.081	0.081	0.003	0.057	0.305
200 mg q.d.	0.763	0.172	0.065	0.115	0.128	0.003	0.069	0.488
400 mg q.d.	0.595	0.187	0.219	0.207	0.236	0.003	0.107	0.844
capmatinib **400 mg** b.i.d.								
50 mg q.d.	0.769	0.196	0.035	0.11	0.101	0.004	0.081	0.382
100 mg q.d.	0.708	0.211	0.081	0.132	0.135	0.004	0.086	0.513
200 mg q.d.	0.614	0.186	0.2	0.194	0.224	0.002	0.099	0.811
400 mg q.d.	0.518	0.123	0.359	0.315	0.348	0	0.141	0.991
capmatinib **600 mg** b.i.d.								
50 mg q.d.	0.655	0.24	0.104	0.152	0.151	0.005	0.104	0.576
100 mg q.d.	0.607	0.213	0.18	0.187	0.201	0.003	0.109	0.744
200 mg q.d.	0.545	0.151	0.305	0.267	0.303	0.001	0.124	0.959
400 mg q.d.	0.495	0.086	0.419	0.379	0.402	0	0.169	1

The model incorporated the existing dose-DLT information from the single agent studies, in which participants have presented good tolerability to the relatively high doses (up to 400 mg b.i.d. for capmatinib tablets and up to 150 mg q.d. for nazartinib capsules) of single agents. Therefore, based on current data, capmatinib tablet 200 mg b.i.d. + nazartinib capsule 50 mg q.d., the starting combination dose satisfies the EWOC criterion.

14.2.4 Hypothetical dose escalation scenarios

In order to show how the Bayesian model reacts, different hypothetical dose escalation scenarios were investigated, following the guidelines presented in Section 6.2.3. The design should make reasonable dose recommendations during the clinical trial based on the observed DLTs. Upon completion of a given cohort, the actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM per EWOC principle as well as on medical review of available clinical and laboratory data.

Based on the prior distribution of DLT rate in Table 14-11, without considering newly available dose-DLT data from single agent studies, Table 14-12 presents the hypothetical dose escalation scenarios for the first few cohorts. Later cohorts are not considered because newly available single agent dose-DLT data are required to update the prior before dose escalation meetings.

Table 14-12 Hypothetical dose escalation scenarios

Scenario	Current status				For next cohort				
	capmatinib (mg b.i.d.)	nazartinib capsule (mg q.d.)	# Participant	# DLT	capmatinib (mg b.i.d.)	nazartinib capsule (mg q.d.)	P(target)	P(over)	Median DLT rate
1	200	50	3	0	200 400	100 50	0.081 0.156	0.006 0.020	0.049 0.069
2	200	50	4	1	200	100	0.234	0.033	0.101
3	200	50	3	2	STOP				
4	200	50	4	2	100	50	0.226	0.027	0.102
5	200 200	50 100	3 3	0 0	200 400	200 100	0.114 0.152	0.021 0.033	0.048 0.060
6	200 200	50 100	3 4	0 1	200 400	200 100	0.274 0.316	0.090 0.111	0.116 0.136
7	200 200	50 100	3 3	0 2	200	50*	0.323	0.020	0.127
8	200 400	50 50	3 4	0 0	400 600	100 50	0.121 0.148	0.018 0.031	0.052 0.063
9	200 400	50 50	3 4	0 1	400 600	100 50	0.313 0.344	0.093 0.142	0.130 0.155
10	200 400	50 50	3 4	0 2	200*	50	0.494	0.123	0.192
11	200 200	50 100	3 5	0 2	200*	50	0.244	0.008	0.112
12	200 200	50 100	4 4	1 1	200	200	0.366	0.172	0.173
13	200 200	50 100	4 4	1 2	200	50	0.460	0.038	0.160
14	200 200 200	50 100 200	3 3 4	0 0 0	400 200	200 400	0.134 0.146	0.065 0.080	0.045 0.051
15	200 200 400	50 100 100	3 3 4	0 0 1	400 600	200 100	0.266 0.307	0.225 0.204	0.207 0.164
16	200 200 200	50 100 200	3 4 4	0 1 1	200	200	0.395	0.091	0.156
17	200 200 200	50 100 200	3 4 4	0 1 2	200	100	0.457	0.032	0.158
18	200 200 400	50 100 100	3 4 4	0 1 2	200	100	0.396	0.029	0.145
19	200 200 200	50 100 200	3 4 5	0 1 2	200	100*	0.401	0.018	0.145
20	200 200 200	50 100 200	3 4 5	0 1 3	200	100	0.585	0.066	0.192

*- In these scenarios, although the model allows to stay at the same dose level combination, since two participants observed DLTs, as per protocol, one of two treatments has to be dose-reduced.

The BLRM is performing reasonably for the hypothetical dose escalation scenarios. In Table 14-12 it can be seen that the recommendations, based on the BLRM and protocol criteria, are in line with clinical sense leading to controlled dose escalation when the observed DLT rate is low (0/3 or 1/4), and a dose de-escalation when 2 or more DLTs are observed at a new dose level.

The dose combinations satisfying the overdose criteria at a specific dose escalation meeting may differ from those presented in Table 14-12 above since newly available dose-DLT data from single-agent studies will be taken into account within the BLRM prior to these meetings.

14.2.5 Starting dose of the nazartinib tablet

Before treating the first cohort of participants with the tablet formulation of nazartinib, the dose-DLT data shown in Table 14-13 will be down-weighted (refer to Section 14.2.2 for the details of the down-weighting process) and incorporated into the BLRM assuming different levels of between trial/formulation heterogeneity (refer to Table 14-6 for details). The updated BLRM will be run to support the starting dose for this new formulation.

Table 14-13 shows the historical data from different studies as of February 2015. Data from [redacted] and [CEGF816X2101] study will need to be further updated by the time of running the BLRM prior to starting the first cohort using nazartinib tablet formulation.

Table 14-13 Available dose-DLT data from single-agent studies as of February 2015

Agent	Study	Dose	# Participants	# DLT
[redacted]				
nazartinib (capsule)	CEGF816X2101	75 mg q.d.	7	0
		150 mg q.d.	14	0
		225 mg q.d.	14	1
		300 mg q.d.	3	0
		350 mg q.d.	6	2
nazartinib (tablet)	CEGF816X2101	225 mg q.d.	6	0

14.2.6 References (available upon request)

EMEA (2007). Guideline on Clinical Trials in Small Populations. Committee for Medicinal Products for Human Use (CHMP).Neuenschwander B, Branson M, Gsponer T (2008). Critical aspects of the Bayesian approach to phase I cancer trials. Statist. Med, 2008; 27: 2420-2439.

Neuenschwander B, Capkun-Niggli G, Branson M, et al (2010). Summarizing historical information on controls in clinical trials. Clinical Trials; 7 (1):5-18.

Rogatko A, Schoeneck D, Jonas W, et al (2007). Translation of innovative designs into phase I trials. J Clin Oncol; 25: 4982-6.

14.3 Appendix 3 - Permitted concomitant medications requiring caution

If a medication that is listed in both Table 14-14 and Table 14-16, more stringent practice shall be applied (that is, the medication shall be prohibited as in Table 14-16).

Table 14-14 Permitted concomitant medications requiring caution with capmatinib and nazartinib

Mechanism of Interaction	Drug Name
Moderate CYP3A4 inhibitor	amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, fosamprenavir, grapefruit juice, imatinib, lomitapide, netupitant, nilotinib, schisandra sphenanthera, tofisopam, verapamil
Moderate CYP3A4 inducer	bosentan, efavirenz, etravirine, genistein, lersivirine, lopinavir, modafinil, nafcillin, [talviraline], ritonavir, semagacestat, talviraline, thioridazine
Sensitive CYP1A2 substrate	alosetron, caffeine, duloxetine, melatonin, ramelteon, selegiline, tacrine, tizanidine
Sensitive CYP2C9 substrate	celecoxib
Sensitive CYP2C19 substrate	clobazam, dexlansoprazole, diazepam, gliclazide, lansoprazole, (R)-lansoprazole, (S)-lansoprazole, (R)-mephobarbital, omeprazole, (R)-omeprazole, pantoprazole, (+) pantoprazole, rabeprazole, tilidine
Sensitive CYP3A4 substrate	alfentanil, almorexant, aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, alpha-dihydroergocryptine, eplerenone, everolimus, felodipine, fluticasone, ibrutinib, indinavir, ivacaftor, levomethadyl, lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, ticagrelor, terfenadine, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, vardenafil, vicriviroc, voclosporin
P-gp substrates	aliskiren, ambrisentan, atorvastatin, atorvastatin acid, azithromycin, cerivastatin, colchicine, CP-481,715, cyclosporine, dabigatran, digoxin, docetaxel, domperidone, doxorubicin, fentanyl, fexofenadine, lapatinib, linezolid, loperamide, maraviroc, nevirapine, paclitaxel, proguanil, quinidine, ranolazine, ritonavir, saquinavir, simvastatin, sirolimus, sofosbuvir, tacrolimus, ticagrelor, voclosporin
P-gp inhibitors	alogliptin, amiodarone, azithromycin, canaglifozin, captopril, carvedilol, clarithromycin, conivaptan, cremophor RH40, curcumin, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fluvoxamine, ginko, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lapatinib, lopinavir/ritonavir, mibefradil, milk thisle, mirabegron, nelfinavir, nifedipine, nitredipine, paroxetine, propafenone, quercetin, quinidine, ranolazine, rifampin, ritonavir, sequinavir/ritonavir, schisandra chinesis extract, simepravir, St. John's wort extract, talinolol, telaprevir, telmisartan, ticagrelor, tipranavir/ritonavir, tolvaptan, valspodar, vandetanib, verapamil, voclosporin
P-gp inducers	avasimibe, carbamazepine, efavirenz, genistein, phenytoin, quercetin, rifampin, St. John's Wort extract
BCRP substrate	atorvastatin daunorubicin, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, SN-38 (irinotecan), ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, topotecan, sulfasalazine
MATE substrate	Metformin, tenfovir

Mechanism of Interaction	Drug Name
OATP substrates	aliskiren, ambrisentan, anacetrapib, atenolol, atrasentan, atorvastatin, bosentan, bromociptine, caspofungin, cerivastatin, celiprolol, danoprevir, empagliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, SN-38, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan, telmisartan, montelukast, ticlopidine
Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: April 2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. The lists provided may not be exhaustive. Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.	

If a medication that is listed in both Table 14-15 and Table 14-17, more stringent practice shall be applied (that is, the medication shall be prohibited as in Table 14-17).

Table 14-15 Permitted concomitant medications requiring caution with capmatinib monotherapy in Phase II Group 5

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, phenytoin, 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

Mechanism of Interaction	Drug Name
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 databases for 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.	

14.4 Appendix 4 - Prohibited concomitant medications

Table 14-16 Prohibited concomitant medications with capmatinib and nazartinib

Mechanism of Interaction	Drug Name
Strong CYP3A4 inhibitor	boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice[10], indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, troleandomycin, danoprevir/ritonavir, eltegravir/ritonavir, indinavir/ritonavir, lopinavir/ritonavir (HIV), saquinavir/ritonavir, tipranoavir/ritonavir
Strong CYP3A4 inducer	avasimibe, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort
CYP1A2 substrate with NTI	theophylline, tizanidine
CYP2C8 substrate with NTI	Paclitaxel
CYP2C9 substrate with NTI	phenytoin, warfarin
CYP2C19 substrate with NTI	(S)-mephenytoin
CYP3A4 substrate with NTI	alfentanil, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine, thioridazine
P-gp substrate with NTI	cyclosporine, digoxin, fentanyl, paclitaxel, phenytoin, quinidine, sirolimus, tacrolimus
Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: April 2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. The lists provided may not be exhaustive. NTI: narrow therapeutic index	
Live vaccines	e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines, COVID-19 vaccines
Medications with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe	amiodarone, anagrelide, arsenic trioxide, astemizole (off US mkt), azithromycin, bepridil (off US mkt), chloroquine, chlorpromazine, cisapride (off US mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US mkt), dronedarone, droperidol, erythromycin, escitalopram, flecainide, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off US mkt), mesoridazine (off US mkt), methadone, moxifloxacin, ondansetron, pentamidine, pimozide, probucol (off US mkt), procainamide (oral off US mkt), quinidine, sevoflurane, sotalol, sparfloxacin (off US mkt), sulpiride (not on US mkt), terfenadine (off US mkt), thioridazine, vandetanib For a comprehensive list of drugs, refer to qtdrugs.org

Table 14-17 Prohibited concomitant medications with capmatinib monotherapy in Phase II Group 5

Mechanism of Interaction	Drug Name
Strong CYP3A 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.	