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Novartis Research and Development

INC280/capmatinib

Clinical Trial Protocol CINC280L12301 / NCT04816214

A phase III randomized, controlled, open-label, multicenter, global study of capmatinib in combination with osimertinib versus platinum - pemetrexed based doublet chemotherapy in patients with locally advanced or metastatic NSCLC harboring EGFR activating mutations who have progressed on prior EGFR-TKI therapy and whose tumors are T790M mutation negative and harbor MET amplification (GEOMETRY-E)

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List of abbreviations

ABCP	atezolizumab (anti-PD-L1) and bevacizumab with carboplatin and paclitaxel
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
ANC	Absolute Neutrophil Count
ART	Antiretrovial Therapy
AST	Aspartate transaminase
ATP	Adenosine Triphosphate
AUC	Area under curve
b.i.d.	bis in die/twice a day
BAL	Bronchoalveolar Lavage
BCG	Bacille Calmette-Guérin
BCRP	Breast Cancer Resistance Protein
BIRC	Blinded Independent Review Committee
BMA	Bone Modifying Agents
BOIR	Best Overall Intracranial Response
BOR	Best Overall Response
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CDS	Core Data Sheet
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central Nervous System
COA	Clinical Outcome Assessment
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	Computerized Tomography
CTCAE	Common Terminology Criteria Adverse Event
[redacted]	[redacted]
CV	coefficient of variation
CVD	Cardio Vascular Diseases
CYP	Cytochrome P450 Enzymes
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DDI	Drug-Drug Interaction

DDS	Dose-Determination Set
DFS	Disease-free survival
DILI	Drug-Induced Liver Injury
DL	Dose Level
DLCO	Diffusing capacity of the Lungs for Carbon monoxide
DLRTM	Dose level review team meeting
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOIR	Duration Of Intracranial Response
DOR	Duration of Response
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	[redacted]
EGFRm	Epidermal growth factor receptor mutated
EORTC	European Organization for Research and Treatment of Cancer
EOT	End Of Treatment
EQ-5D-5L	EuroQoL-5 Dimension-5 Level
ERCP	Endoscopic retrograde cholangiopancreatography
eSource	Electronic Source
ET	Extension Treatment
FACT	Functional Assessment of Cancer Therapy
FAS	Full Analysis Set
FAS-BM	Full Analysis Set – Brain Metastases
FBrSI	FACT-Brain Symptom Index
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose- Positron Emission Tomography
FFPE	Formalin Fixed Paraffin Embedded
FISH	Fluorescence In Situ Hybridization
FPFV	First Patient First Visit
FSH	Follicle Stimulating Hormone
FUP	Follow-Up Period
G-CSF	Granulocyte Colony-Stimulating Factor
GCN	Gene Copy Number
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
h	Hour
HBsAg	Hepatitis B surface antigen

HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HER2	Human Epidermal growth factor Receptor 2
HEV	Hepatitis E Virus
Hgb	Hemoglobin
HGF	Hepatocyte Growth Factor
HGRAC	Human Genetic Resource Administration of China
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
HSV	Herpes Simplex Virus
i.v.	Intravenous
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICI	Immuno Checkpoint Inhibitors
IDCR	Intracranial disease control rate
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUS	Intra-uterine System
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LPLV	Last Patient Last Visit
LVEF	Left ventricular ejection fraction
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
MET	Mesenchymal-to-Epithelial Transition factor
mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple gated acquisition
NCCN	National Comprehensive Cancer Network
[redacted]	[redacted]
NSCLC	Non-small-cell lung cancer

NT	Non-target
NT-proBNP	N-terminal pro-brain natriuretic peptide
NTI	Narrow Therapeutic Index
OHP	Off-site healthcare Professional
OIRR	Overall Intracranial Response Rate
ORR	Overall Response Rate
OS	Overall survival
P-gp	P-glycoprotein
PAS	Pharmacokinetic Analysis Set
PD	Progressive disease
PD-L1	Programmed Death-Ligand 1
PFS	Progression free survival
PFS2	Progression-Free Survival after next line of treatment
PK	Pharmacokinetic(s)
PLT	Platelet
PR	Partial Response
PRO	Patient Reported Outcomes
PT	Prothrombin time
QD	Once a day
QLQ	Quality of Life Questionnaire
QMS	Quality Management System
[redacted]	[redacted]
QTcF	Fridericia QT correction formula
R Value	ALT/ALP x ULN
RANKL	Receptor activator of nuclear factor kappa-B ligand
RANO	Response assessment in neuro-oncology
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
ROS1	c-ros oncogene 1
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SJS	Stevens-Johnson Syndrome
SOCs	System Organ Classes
TFQ	Trial feedback questionnaires
TKI	Tyrosine Kinase Inhibitors
TSH	Thyroid Stimulating Hormone
TTE	Transthoracic echocardiography
TTIR	Time To Intracranial Response
TTR	Time To Response

Ty21a	Live-attenuated TY2 strain of S. Typhi
ULN	upper limit of normal
USA	United States of America
USPI	United States Prescribing Information
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., 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 intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from 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 at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the ICH E9 (R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable
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
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participants allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home

Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g., Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home. Add in specific terms used for off-site health professionals in the protocol only where you are sure this will be the case 100% of the time, for example if blood samples may be collected by an Off-site Research Nurse (ORN) or Off-site Phlebotomist use the broader term Off-site Healthcare Professional (OHP) to cover all situations., e.g., Off-site Research Nurse (ORN): Refer to Off-site healthcare professional
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations
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	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant’s health condition without amendment or interpretation of the participant’s report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias
Randomization number	A unique identifier assigned to each randomized participant
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 in the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
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 clinical trial is defined as the signature of the informed consent by the first participant
Study device	Study device is a medical device (marketed or investigational) that is used in a circumstance that makes it part of the investigation
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts

Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event
Withdrawal of study consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

Amendment 02 (03-Mar-2022)

Amendment rationale

As of 03-Mar-2022, 3 patients have been enrolled in the study.

The main purpose of this amendment is to include the possibility for participants who progressed in the platinum – pemetrexed chemotherapy arm to crossover to the capmatinib + osimertinib arm. The new treatment period has been named Extension Treatment. The decision to allow crossover of participants who have progressed on chemotherapy arm is due to the fact that this population does not have many effective therapeutic alternatives, and the combination of capmatinib + osimertinib has shown significant preliminary meaningful clinical activity in this MET amplified NSCLC population.

The main updates cover the following:

- Inclusion of an additional study treatment period called Extension Treatment (ET) for participants allowed to crossover from platinum – pemetrexed chemotherapy arm to capmatinib + osimertinib treatment arm. Participants will be allowed to crossover only after BIRC confirmed, RECIST 1.1-defined PD and after meeting eligibility criteria outlined in Section 6.1.5.2.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version using strikethrough red font for deletion and red underline for insertions as described below:

- Abbreviation for Bone Modifying Agents (BMA), Extension Treatment (ET) and Off-site healthcare Professional have been added to the List of abbreviations
- The Glossary of terms has been updated as per Novartis Protocol template version 5
- ET has been added to the Protocol Summary in the Study Design subsection
- "Platinum – pemetrexed doublet based chemotherapy" has been corrected to "platinum – pemetrexed based doublet chemotherapy" throughout the document when applicable
- In Section 3, the possibility for participants to crossover from platinum – pemetrexed chemotherapy arm to capmatinib + osimertinib treatment arm has been added and eligibility criteria have been defined
- In Section 3, clarification on safety follow-up and survival follow-up for participants crossing over to capmatinib + osimertinib therapy has been added
- Figure 3-2 has been updated to include the crossover to capmatinib + osimertinib arm
- The crossover has been added to the Rationale for study design in Table 4-1
- Section 4.5 was updated to explain the risks associated with the investigational status of the centralized MET amplification assay
- A statement has been added in Section 4.5.1 related to risks associated with COVID-19 while on capmatinib treatment
- The range of definition of high frequency hearing loss has been corrected in Section 4.5.3 from 4000-8000 Hz to 2000-8000 Hz
- A clarification has been added in Section 5.1, inclusion criterion # 5 related to the possibility to have central T790M testing when local T790M result is not available (only applicable for randomized part)

- Wording has been revised for inclusion criterion # 7 in Section 5.1 to add clarity
- Wording has been revised for exclusion criterion # 18 and # 19 in Section 5.2 to add clarity, and as per Novartis Protocol template version 5
- Wording of Table 6-1 has been revised as per Novartis Protocol template version 5
- Crossover wording has been added in Section 6.1.3 and Section 6.3.2
- In Section 6.1.5, the possibility of participants to crossover to capmatinib + osimertinib arm has been added
- In Section 6.1.5.1, the possibility of participants who crossover to ET to receive treatment beyond progression has been added
- Section 6.1.5.2 (Crossover to capmatinib in combination with osimertinib therapy) has been added to the protocol. The Section describes in details the eligibility criteria that participants have to fullfil to be allowed to crossover and defines the EOT visit to be performed in case of crossover
- Section 6.2.1.2, Section 6.5.5.1 , Section 6.7.1.1 and Section 7 have been updated as per Novartis Protocol template version 5
- Information on ET visit windows have been added to Table 8-1
- Table 8-3 has been updated to include the additional ET period and the related assessments which will be performed for participants who crossover to ET. Visit numbers have also been updated accordingly
- A statement in Table 8-3 has been added to clarify that participants who crossover must be consented under Protocol Amendment 02
- Language in Section 8.1 has been revised to clarify that central MET ampfliciation test is investigational and sufficiently validated for the purposes of identifying patients for this study
- A statement has been added in Section 8.1 to confirm that participants who crossover to ET do not have to re-confirm eligibility with regards to molecular testing
- A clarification on MET amplification testing requirements has been added in Section 8.1
- In Table 8-2, Table 8-3 and Section 8.2, collection of PD-L1 status has been added
- A clarification has been added in Table 8-2, Table 8-3, Table 8-14 and Table 8-15 where tumor samples for pre-screening can be collected during or after progression from prior EGFR TKI treatment (not only after progression)
- In Section 8.3.1.3, for participants who crossover, instructions for determining disease progression and clarification on imaging assessments have been added
- In Section 8.4.1 and in Table 8-3, a statement explaining local laboratory evaluations for ET has been added
- In Table 8-9 and in Section 8.4.2, ET period timelines for ECGs have been included
- Section 8.4.3.1 has been updated as per Novartis Protocol template version 5 to add clarity on fertility assessment
- The possibility to have central T790M testing when local T790M result is not available has been removed from Table 8-2 and Table 8-14, since it is only applicable for randomized phase

[redacted]

- Language of Section 8.5.1 has been modified as per Novartis Protocol template version 5
- In Section 8.5.1 and in Table 8-3, a clarification has been added for PROs collection stating that for participants who crossover to ET, PROs will be only collected post-platinum – pemetrexed progression
- In Section 8.5.2, a statement has been added to clarify that participants crossing over ET do not undergo any scheduled PK sample collection

[redacted]

- In Section 8.5.3.1, wording has been revised to add clarity
- In Section 8.5.3.2, clarification on blood samples collection for Part 2 has been added
- Language of Section 9.1.2 and Section 9.1.3 has been updated as per Novartis Protocol template version 5
- The collection of PROs in case of death has been removed from Section 9.2.2
- In Section 9.2.3, a clarification on survival follow-up for participants who crossover has been added
- Section 10.1.3 updated to comply with BfArM requirements regarding SAE reporting in Germany
- Section 10.1.3 updated for SAE collection schedule to be consistent with protocol
- In Section 10.1.3, wording has been revised for participants' pre-screening procedures in regards of molecular pre-screening ICF signature
- Pregnancy reporting for ET has been added in Section 10.1.4
- In Section 12.5.1, a statement has been added related to the possibility of assessing PFS2 on participants who crossover if a sufficient number of participants fit specific criteria
- In Section 12.5.2, clarification on observation period for participants who crossover to ET has been added
- Language in Section 13.1 has been updated as per Novartis Protocol template version 5
- Language in Section 13.5 was updated to add flexibility for Patient Engagement initiatives

In addition, as part of this amendment, minor editorial changes to improve flow and consistency have been made throughout the protocol.

IRBs/IECs

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

Amendment 01 (14-Sep-2021)

Amendment rationale

As of 14 Sep-2021, enrollment has not yet started.

The main purpose of this amendment is to add clarity on few sections as suggested by some health authorities. The main updates cover the following:

- Revision of inclusion- exclusion criteria.
  - Remove the requirements to have a T790M negative results for participant previously treated with osimertinib based on the concept that T790M mutation is an acquired resistance mechanism of 1st or 2nd generation EGFR TKI rather than osimertinib.
  - Allow patients who previously received 3rd generation EGFR TKIs other than osimertinib to participate in this study.
  - Exclude participants with known druggable molecular alterations who might be candidates for alternative targeted therapies.
  - Exclude participants with known EGFR T790M positive status.
  - Exclude participants who received live vaccines within 30 days prior to the first dose of study treatment.
- Revision of the DLT wording criteria.

[redacted]

Changes are implemented throughout the document to reflect the updated Novartis protocol template. In addition, a new ICF is added to capture the participant consent to continue the combination treatment (capmatinib-osimertinib) following disease progression.

Few minor editorial changes and corrections were applied throughout the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough red font for deletions and red underline for insertions as described below.

- Add to the Background Section 1.1 updated information concerning other 3rd generation EGFR TKIs that have demonstrated similar efficacy compared to osimertinib which are expected to be approved in China.

[redacted]

- Update the Protocol summary to align with the changes made in the protocol and to correct a typo error stating that effect of combination treatment as compared to platinum-pemetrexed on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL) by evaluating the change from baseline and time to symptom

deterioration "end point" will be applicable for EORTC QLQ-C30, QLQ-LC13 and NCCN FBrSI questionnaires, instead of EQ-5D-5L questionnaire as previously stated. The same is reflected in Table 2-1.

- Clarification for the intercurrent event related to start of new anti-cancer therapy (for ORR and OIRR) are added to Section 2.2.
- Modify Section 3 and Section 4.1 to reflect the updated inclusion exclusion criteria. The text was updated throughout the document to include patient who had progressed on other third generation EGFR TKI other than osimertinib. An additional threshold of 10% for participant who progressed on other third generation EGFR TKI other than osimertinib was added. It was additionally stated that participants previously treated with osimertinib are not required to have central confirmation of EGFR T790M negative tumor status however those with known T790M positive tumor status are excluded from the study. The stratification factors were also updated throughout the text accordingly.
- Update Figure 3-1 Part 1: Run-in Part to remove the PRO assessment that are not applicable to this part of the trial.
- The Rationale wording was clarified in Section 4 and throughout the text to state that it is due to the unmet medical need and lack of a current targeted approved therapy for the MET amplification that is one of the leading mechanisms of resistance to EGFR TKI in EGFR mutated NSCLC
- Clarify the DMC meeting schedule to ensure timely safety monitoring for participants treated with the combination (capmatinib + osimertinib) in Section 4.5 Risks and benefits.
- Update Sections 4.5.2 and Section 6.5.4 to add further clarification concerning additional precaution for the study treatment.
- Add Section 4.5.3 Cisplatin, carboplatin and pemetrexed in order to provide further clarification to outline the precautions related to the comparator therapy in the protocol.
- Clarified the wording in inclusion criterion (#3) in Section 5.1 to add "chemoradiation" to "curative surgery and radiation".
- Update inclusion criterion (#5) in Section 5.1 to clarify the types of EGFR mutations which are known to be associated with TKI sensitivity, the specifications for local testing and which participants are required to have confirmed T790M negative tissue status. Clarify the sample types for MET amplification in both run-in and randomization parts.
- Clarify inclusion criterion (#7) in Section 5.1 by removing the word "maximum" describing participants who must have failed one prior line of therapy and updating to include all of previous of EGFR TKI treatment for advanced/metastatic disease (stage IIIB/IIIC [not amenable to curative surgery, chemoradiation or radiationor stage IV NSCLC) used per local standard of care, instead of either 1st/2nd generation EGFR TKI or osimertinib all over the document and title. It was also clarified that adjuvant osimertinib therapy will count as prior line of EGFR TKI treatment if relapse occurs during the adjuvant osimertinib therapy.
- Exclusion criteraion (#11) in Section 5.2 was udpated to read as follow: Treatment with a prior 1st or 2nd generation EGFR TKIs (e.g., erlotinib, gefitinib, afatinib, dacomitinib) osimertinib or another 3rd generation EGFR TKIs such as almonertinib and furmonertinib within 14 days or approximately 5x half-life, whichever is shorter, of the first dose of study treatment.

- Remove "follow chemotherapy schedule" from exclusion criterion (#14) in Section 5.2
- Adjust the exclusion criterion (#15) in Section 5.2 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 randomization. Additional criteria were clarified for exclusion of HIV patients.
- Exclusion criterion (#16) in Section 5.2 was updated to add "contraindications" to read: Participants with known hypersensitivity or contraindications to capmatinib or osimertinib or carboplatin or pemetrexed or cisplatin, or any excipient of these agents
- Adjust the exclusion criterion (#18) for women of childbearing potential in Section 5.2 to add the use of hormonal contraceptive not prone to DDI and to specify that the use of hormonal contraceptives should be combined to the use of condom, in order to minimize the risk of exposure.
- Add an additional exclusion criterion (#20) in Section 5.2 to exclude participants with known druggable molecular alterations who might be candidates for alternative targeted therapies, as per the local regulations and treatment guidelines.
- Add an additional exclusion criterion (#21) in Section 5.2 to exclude participants with documented EGFR genetic aberration mediating resistance to previous treatment with a 3rd generation EGFR TKI or any other known genetic aberration concomitant to MET amlification that could negatively impact the treatment outcome of capmatininb in combination with osimertinib.
- Add an additional exclusion criterion (#22) in Section 5.2 to exclude participant with known EGFR T790M positive status by either tissue or blood after progression on 1st, 2nd or 3rd generation EGFR TKIs including osimertinib.
- Add an additional exclusion criterion (#23) in Section 5.2 to exclude participants who received live vaccines within 30 days prior to the first dose of study treatment.
- Stratification factor for patients in randomized phase has been updated from "prior treatment with osimertinib" to "prior treatment with EGFR TKIs" in Protocol Summary, Section 3, Section 6.3.2 and Section 12.4.2.
- Add wording to Section 6.1.3 to provide additional guidance on chemotherapy treatment as per the local guidelines.
- Update Section 6.1.5.1, Table 8-2, Table 8-3 and Section 7 to include an additional participant consent to continue on the study treatment beyond progression only for patient treated with the combination treatment (capmatinib + osimertinib).
- Update Section 6.2.2 to add live vaccines into prohibited medications during study treatment and 30 days after the last dose of study treatment.
- Clarify that the threshold for enrollement of different population will be monitored throught the IRT system in Section 6.3.2
- Clarify the treatment blinding wording in Section 6.4
- Update criteria for defining DLTs in Table 6-4 to include neutropenia grade 4 regardless of duration, thrombocytopenia grade 4 regardless of duration or bleeding, laboratory abnormalities ≥ grade 3 that result in hospitalization and any death not clearly related to the underlying disease or extraneous causes.

- Add to Section 6.5.4 and Table 6-7, a clarification that for confirmed pneumonitis and interstitial lung disease, both capmatinib and osimertinib should be discontinued.
- Update Section 6.7 Preparation and dispensation, to exclude platinum pemetrexed from applicable study treatment to be shipped to the participant home as per the local regulations in case of public health emergency as declared by local or regional authorities.
- Update Section 6.5.4 to remove dose re/escalation of study treatment.
- Update Section 6.7.1.1 with instructions on how to handle study treatment according to updated Novartis Protocol template version 4.
- Update Section 6.7.2.1.1 in order to be consistent with the Table 8-2 and Table 8-3 concerning the food consumption information to be captured on the CRF; information of whether capmatinib was administered with or without food must be recorded in the appropriate eCRF.
- Update Table 6-8 to add clarity on measures related to dose modification for capmatinib, if osimertinib is permanently discontinued and capmatinib continued as monotherapy.
- The molecular Pre-screening wording was udpated in Section 8.1 to reflect the inclusion and exclusion updated criteria and to add information about the validated accepted tests. Clarification was also added to indicate that previously treated participant with osimertinib do not require EGFR T790M negative status confirmation.
- Update ECHO/MUGA assessment window from ≤ 72h before C1D1 to ≤ 15 days before C1D1 in Section 8.4.2.1 and Table 8-1, Table 8-2 and Table 8-3.
- [redacted]
- Update Table 8-2 and Table 8-3 to remove ECOG assessment at C1D15 time point.
- Table 8-7 has been updated to include red blood cells analysis in Hematology panel as per updated Novartis Protocol template version 4.
- [redacted]
- Replace the 72 hrs window with a 15 days window prior to study medication/C1D1 for Cardiac imaging assessment (Table 8-2 and Table 8-3, and Section 8.4.2.1).
- Adjust the typo error (30% instead of 25%) in the hypothesis for OIRR in Section 12.5.1.1 to match what is correctly stated in Section 12.8.2 and adjust the PFS event to 162 instead of 177 in Section 12 Data analysis and statistical methods.
- Update the wording in Section 12.5.1.2 to read “participants will also be censored if they did not have an event” instead of “Participants will also be censored for death due to other causes” to be consistent within the section and aligned with internal Novartis RANO-BM guidelines.
- [redacted]
- “Patients” and “Subjects” were replaced with the term “Participants” where applicable.
- Glossary of terms was updated to reflect changes in the new Novartis Protocol template version 4.

- Rationale was added in the Protocol Summary as per updated Novartis Protocol template version 4.
- Title of Section 2 was modified to "Objectives, endpoints and estimands" and Table 2-1 was updated as per updated Novartis Protocol template version 4.
- The definition of estimand was added to Section 2.1
- Exclusion criterion #18 updated as per updated Novartis Protocol template version 4 to include the definition of women not considered of childbearing potential.
- Heading of Table 6-1 was modified as per updated Novartis Protocol template version 4.
- Abbreviations were updated to reflect additional wording and were clarified as per updated Novartis Protocol template version 4 in Section 6.5.5.1.
- Section 6.6.1, Section 6.7, Section 6.7.1.1, Section 7, Section 8.4.1, Section 8.4.2 and Section 8.4.3: language related to Public Health Emergencies and potential off-site study visits have been added as per updated Novartis Protocol template version 4.
- Discontinuation language was modified in Section 8 and Section 9 as per updated Novartis Protocol template version 4.
- Section 8.3.1.2, Section 9.1.1 and Section 9.1.2: Withdrawal of consent language was modified to include use of data and biological samples as per updated Novartis Protocol template version 4.
- Section 8.4.2 was modified as per updated Novartis Protocol template version 4 for clarity and standardization across divisions. In addition, transmission of unscheduled ECG was updated to reflect that the ECG collection strategy applies to all parts of the trial and not the randomization part only.
- In Section 9, language for participant discontinuation has been modified as per updated Novartis Protocol template version 4.
- Title of Section 10 was modified to "Safety monitoring, reporting and committees" as per updated Novartis Protocol template version 4.
- In Section 10.1.2 redundant text has been deleted.
- In Section 10.1.3, SAE reporting instructional text has been modified as per updated Novartis Protocol template version 4.
- In Section 10.1.4, Pregnant Participant language has been modified for clarity as per updated Novartis Protocol template version 4.
- In Section 12.2 and Section 12.3, text has been modified as per updated Novartis Protocol template version 4.
- Title of Section 12.4 has been modified to "Analysis supporting primary objectives" as per updated Novartis Protocol template version 4.
- Title of Section 12.4.1 has been modified to "Definition of primary endpoint(s)" as per updated Novartis Protocol template version 4.
- Title of Section 12.4.3 has been modified to "Handling of intercurrent events of primary estimand" as per updated Novartis Protocol template version 4.
- Title of Section 12.4.5 has been modified to "Sensitivity analyses" as per updated Novartis Protocol template version 4.

- Title of Section 12.5 has been modified to “Analysis supporting secondary objectives” as per updated Novartis Protocol template version 4.
- In Section 12.5.2 text was modified for vital signs, 12-lead ECG and Clinical laboratory evaluations as per updated Novartis Protocol template version 4.
- Section 13.5 related to Participant Engagement was added as per updated Novartis Protocol template version 4.
- Minor typographical erros corrected allover the document.

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.

Protocol summary

Protocol number	CINC280L12301
Full Title	A phase III randomized, controlled, open-label, multicenter, global study of capmatinib in combination with osimertinib versus platinum - pemetrexed based doublet chemotherapy in patients with locally advanced or metastatic NSCLC harboring EGFR activating mutations who have progressed on prior EGFR-TKI therapy and whose tumors are T790M mutation negative and harbor MET amplification (GEOMETRY-E)
Brief title	Study of safety and efficacy of capmatinib in combination with osimertinib compared to platinum - pemetrexed based doublet chemotherapy in patients with locally advanced or metastatic non-small cell lung cancer harboring EGFR activating mutations, MET amplification and T790M negative who have progressed on prior EGFR-TKI therapy
Sponsor and Clinical Phase	Novartis, Phase III
Investigation type	Drug
Study type	Interventional
Purpose	The purpose of this prospective, randomized, controlled, open-label, multicenter, global phase III study is to evaluate the efficacy and safety of capmatinib in combination with osimertinib compared to platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy as second line treatment in patients with locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC with Epidermal Growth Factor Receptor (EGFR) activating mutation (ie. L858R and/or ex19del), T790M negative, MET amplified (defined as Gene Copy Number [GCN] ≥ 5 per central Novartis laboratory) who have progressed following 1st/2nd generation EGFR Tyrosine Kinase Inhibitors (TKIs) treatment, osimertinib or other 3rd generation EGFR TKIs used per local standard of care.
Primary Objective(s)	The primary objective of run-in part (part 1) of this study is to confirm the recommended dose of capmatinib in combination with osimertinib for the randomized part (part 2). The primary objective of the randomized part (part 2) is to compare the efficacy of capmatinib in combination with osimertinib as compared to platinum - pemetrexed, by comparing progression-free survival (PFS) by blinded independent review committee (BIRC) according to Response Evaluation Criteria In Solid Tumors (RECIST 1.1) between treatment arms
Secondary Objectives	Key secondary (randomized part) • To compare the overall response rate (ORR) per RECIST 1.1 by BIRC of capmatinib in combination with osimertinib as compared to platinum - pemetrexed • To compare the overall intracranial response rate (OIRR) by BIRC as per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria of capmatinib in combination with osimertinib as compared to platinum - pemetrexed, in participants with Central Nervous System (CNS) lesions Secondary (run-in part) • To characterize the safety and tolerability of capmatinib in combination with osimertinib based on the incidence, type and severity of adverse events, change in laboratory values, vital signs, liver and cardiac assessment • To characterize the pharmacokinetics of capmatinib, osimertinib, and osimertinib's active metabolites (AZ5104 and AZ7550) in combination setting by assessing plasma Pharmacokinetic(s) (PK) concentrations and derived PK parameters • To assess the tumor response of capmatinib in combination with osimertinib calculated by RECIST 1.1 by investigator Other Secondary (randomized part) • To assess the anti-tumor activities of capmatinib in combination with osimertinib as compared to platinum - pemetrexed (e.g., duration of response (DOR), Time to response (TTR), Disease control rate (DCR), all by BIRC per RECIST 1.1) • To assess PFS2 (PFS after next-line of treatment) based on local investigator assessment

	• To characterize the pharmacokinetics of capmatinib, osimertinib, and osimertinib's active metabolites (AZ5104 and AZ7550) in combination setting by assessing plasma PK concentrations • To evaluate overall survival (OS) in participants treated with capmatinib in combination with osimertinib as compared to platinum - pemetrexed • To evaluate the safety profile of capmatinib in combination with osimertinib as compared to platinum - pemetrexed • To assess the effect of capmatinib in combination with osimertinib as compared to platinum-pemetrexed based doublet chemotherapy on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL) by evaluating the change from baseline in European Organization for Research and Treatment of Cancer (EORTC) QLQ-LC13, QLQ-C30, EuroQoL-5 Dimension-5 Level/EQ-5D-5L, and NCCN Fact Brain Symptoms Index questionnaires and time to symptom deterioration for EORTC QLQ-C30, QLQ-LC13 and NCCN FBrSI questionnaires • To assess intracranial anti-tumor activity of capmatinib in combination with osimertinib as compared to platinum-pemetrexed in participants with Central Nervous System (CNS) lesions at baseline (e.g., Duration of intracranial response (DOIR), time to intracranial response (TTIR) and intracranial disease control rate (IDCR), all by BIRC as per RANO-BM criteria)
Study design	This is a multicenter, open-label, randomized, active-controlled, global phase III study that will enroll adult participants with locally advanced or metastatic NSCLC with EGFR activating mutation, T790M negative, MET amplified who have progressed following EGFR TKIs (EGFR TKIs can be 1st and 2nd generation EGFR TKIs, osimertinib or other 3rd generation EGFR TKIs used per local standard of care). Randomization of participants who have progressed on prior line with osimertinib will be a minimum of 50% of the planned total number of participants) while for the other third generation EGFR TKI will be maximum of 10% of the planned total number of participants. The study will consist of an initial safety run-in part to evaluate the safety and tolerability of capmatinib in combination with osimertinib and to confirm the recommended dose for the randomized part, and a randomized part that will evaluate the efficacy and safety of capmatinib in combination with osimertinib compared to platinum (cisplatin or carboplatin) – pemetrexed based doublet chemotherapy as second line treatment. Participants who progressed in the platinum – pemetrexed arm will be allowed to crossover to capmatinib + osimertinib therapy. The study will enroll approximately 10 to 20 participants in the run-in part and approximately 225 participants in the randomized part. Participant's respective treatment (either with capmatinib in combination with osimertinib, or with platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy) will be continued until participant experiences any of the following: documented disease progression by RECIST 1.1 (as assessed by the investigator in the run-in part, and as assessed by the investigator confirmed by BIRC in the randomization part), withdrawal of consent, pregnancy, lost to follow-up, or death. The combination treatment of capmatinib + osimertinib may be continued beyond initial disease progression as per RECIST 1.1 if, in the judgement of the investigator, there is evidence of clinical benefit, and the participant wishes to continue on the study treatment. After treatment discontinuation, all participants will be followed for safety evaluations during the safety follow-up period
Rationale	The rationale for investigating the anti-cancer activity of capmatinib in combination with osimertinib is due to the unmet medical need and lack of a current targeted approved therapy for MET amplification that is one of the leading mechanisms of resistance to EGFR TKI in EGFR mutated NSCLC. Few options to date are available for this population with limited benefit, in particular in the T790M negative setting. Proof of concept for capmatinib in combination with EGFR TKIs in MET positive EGFR mutated post-EGFR TKI NSCLC setting has been demonstrated with both first-generation EGFR TKI (gefitinib) and 3rd generation EGFR TKI (EGF816).

Study population	This study will enroll adult male and female participants with EGFR activating mutation (i.e., L858R and/or ex19del), T790M negative, advanced (stage IIIB, IIIC or IV) NSCLC harboring MET amplification as determined by a Novartis central molecular laboratory and who have progressed following 1st/2nd generation EGFR TKIs, osimertinib or other third generation EGFR TKIs used per local standard of care.
Key Inclusion criteria	• Stage IIIB/IIIC (not amenable to curative surgery, chemoradiation or radiation) or stage IV NSCLC at the time of study entry • Histologically or cytologically confirmed diagnosis of NSCLC with EGFR mutations known to be associated with EGFR TKI sensitivity, EGFR T790M negative, and MET gene amplification defined as IHC 3+ for the Run-In part (defined as ≥ 50% of cells staining with high intensity) and/or MET Gene Copy Number ≥ 5 will be utilized as study entry parameters by local test in tissue or blood. For the Randomized part, it should be defined as Gene Copy Number (GCN) ≥ 5 per central Novartis designated laboratory result from tissue sample test • Mandatory provision of a formalin-fixed, paraffin embedded tumor tissue sample (a newly obtained tumor sample, or archival tumor block/slides taken after progression on prior line of EGFR TKI) • Participants must have progressed on one prior line of therapy (either to 1st/2nd generation EGFR TKIs, osimertinib, or other 3rd generation EGFR TKIs used per local standard of care for advanced/metastatic disease and must be eligible candidates for platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy • At least one measurable lesion as defined by RECIST 1.1 • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
Key Exclusion criteria	• Prior treatment with any MET inhibitor or Hepatocyte Growth Factor (HGF)-targeting therapy • 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 • Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention) • Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome • Treatment with a prior 1st or 2nd generation EGFR TKIs (e.g., erlotinib, gefitinib, afatinib, dacomitinib), osimertinib or another third generation EGFR TKIs such as almonertinib and furmonertinib, within 14 days or approximately 5x half-life, whichever is shorter, of the first dose of study treatment • Unable or unwilling to swallow tablets as per dosing schedule
Study treatment	Capmatinib (INC280) + osimertinib or platinum - pemetrexed based doublet chemotherapy
Efficacy assessments	• Tumor assessment by RECIST 1.1 performed every 6 weeks for the first 18 months starting at C3D1, then every 12 weeks until progressive disease (PD) determined using RECIST 1.1 by investigator (run-in part) or by investigator and confirmed by BIRC (randomized part) • CNS lesions assessed by BIRC based on RANO-BM criteria • survival status collected every 12 weeks regardless of treatment discontinuation reason (except if consent is withdrawn or participant is lost to follow-up) until death, lost to follow-up, or withdrawal of consent for survival follow-up (randomized part only)
Pharmacokinetic assessments	Blood samples will be collected from all participants who receive capmatinib and osimertinib to assess plasma PK of capmatinib, osimertinib and osimertinib's active metabolites (AZ5104 and AZ7550) at the following time points: • Cycle 1 Day 1 • Cycle 1 Day 2 and Cycle 1 Day 15 (only for run-in part)

	• At Day 1 of Cycles 2 (only for randomized part), C3, C4 and C6 (applicable for both run-in and randomized parts) No blood samples will be collected to assess PK for participants in ET period
Key safety assessments	• Laboratory assessments, including hematology, chemistry, urinalysis, coagulation, Human Immunodeficiency virus (HIV) testing (where locally required), pregnancy test (for women of child-bearing potential) • Physical examination • Vital signs • Body weight and height • Electrocardiogram (ECG) and cardiac imaging Multigated Acquisition Scan (MUGA) • Collection of Adverse Events (AE) and Serious Adverse Events (SAE)
Other assessments	• Patient Reported Outcomes (PRO): EORTC QLQ-C30, QLQ-LC13, NCCN FACT Brain Symptom Index and EQ-5D-5L
Data analysis	The primary objective is to evaluate whether capmatinib in combination with osimertinib prolongs PFS by BIRC according to RECIST 1.1 compared to platinum-based chemotherapy. The primary endpoint for the safety run-in phase is the incidence of Dose Limiting Toxicity (DLT) during cycle 1. The dose recommendation decision will be based on the following criteria: • At least six evaluable participants treated at this dose and regimen • No more than two DLT have been observed out of six evaluable participants • It is the dose recommended for participants after review of all clinical data by Novartis and Investigators in a dose level review team meeting If one of the conditions specified above is not satisfied, dose confirmation cannot be declared and a second cohort may be treated at the lower dose level with capmatinib (400 mg b.i.d.) and osimertinib (40 mg q.d.). The same criteria are applied for this new dose and regimen. If dose confirmation cannot be declared on this lower dose, the randomized part cannot start and the study will end. For randomized part, the primary efficacy analysis to test these hypotheses and compare the two treatment groups will consist of the stratified log-rank test at an overall one-sided 2.5% significance level. The following null and alternative hypothesis will be tested to address the primary efficacy objective for PFS based on BIRC as per RECIST 1.1:H01: $\theta 1 = 1$ vs. HA1: $\theta 1 < 1$ where $\theta 1$ is the PFS hazard ratio (capmatinib in combination with osimertinib versus platinum pemetrexed based chemotherapy). The stratification will be based on the stratification factors assigned at randomization (presence of brain metastasis at baseline (presence vs absence) and previous treatment with 3rd generation EGFR TKIs (yes vs no). The PFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for PFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test
Key words	Capmatinib, osimertinib, platinum-pemetrexed, Non-small-cell lung cancer (NSCLC), EGFR

1 Introduction

1.1 Background

1.1.1 Non-small cell lung cancer (NSCLC) treatment landscape

Lung cancer is the most commonly diagnosed 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 (WHO 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).

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

Mechanisms of oncogenesis in lung cancer have been largely deciphered over the past 20 years. The concept of "oncogene addiction" refers to tumor-cell dependence on the specific activity of an activated or overexpressed oncogene. The main oncogenic drivers in the field of thoracic oncology are mutations of EGFR, and ALK (Anaplastic Lymphoma Kinase) rearrangements. Activating mutations in EGFR and ALK translocations have been the first molecular drivers proving to be strong predictors of response to targeted therapies such as EGFR and ALK Tyrosine Kinase Inhibitors (TKIs) showing improved efficacy and better tolerance when compared to standard chemotherapy in patients harboring EGFR activating mutations and ALK translocations and have become standard of care in both the pretreated and treatment naive settings (Ettinger 2010, Zhou et al 2011, Fukuoka et al 2011, Shaw et al 2013, Rosell et al 2012, Sequist et al 2013, Solomon et al 2014, NCCN 2021). Activating mutations in the EGFR gene are observed frequently in patients with lung adenocarcinoma, but are rare in squamous cell carcinoma. Approximately 50% of Asian adenocarcinoma patients carry EGFR mutations, including 50.2% of Chinese patients (Shi et al 2015), compared with 10–20% of Caucasian adenocarcinoma patients (Harrison et al 2020). The most common EGFR mutations, also known as the classical mutations, are inframe deletions in exon 19 (del19; 49–72% of EGFR mutations) and a nucleotide substitution within codon 858 of exon 21 (L858R; 28–43%). Other EGFR mutations have been detected in 7–23% of patients and include the G719X (~30% of uncommon mutations), L861Q (13–35%), and S768I (~5%) mutations.

Management of NSCLC harboring mutations in the epidermal growth factor receptor (EGFR) gene has been transformative in recent years. The next clinical challenge for this disease is to overcome or prevent drug resistance.

Three generations of EGFR TKIs are now approved for use in EGFR mutation-positive NSCLC; the first-generation agents erlotinib, gefitinib, and icotinib; the second-generation ErbB family blockers afatinib and dacomitinib; and most recently, osimertinib, a third-generation EGFR TKI.

First- and second-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are effective as first-line treatment for advanced NSCLC harboring activating EGFR mutations (e.g., deletions in exon 19 and the exon 21 L858R mutation). EGFR T790M mutation emerges following EGFR-TKI therapy, and accounts for 55% of mechanisms of acquired resistance to first- and second-generation EGFR-TKIs (Liao et al 2019). Osimertinib monotherapy is currently widely recommended second-line treatment for EGFR T790M mutation-positive (T790M-pos) NSCLC, and is also the recommended first-line treatment for patients with locally advanced or metastatic EGFR mutation-positive NSCLC (Liao et al 2019). Other 3rd generation EGFR TKIs such as almonertinib and furmonertinib have demonstrated similar efficacy compared to osimertinib and are expected to be approved in China for the treatment of patients with first line EGFR mutated NSCLC.

In addition, recent results from the Phase III ADAURA trial showed that osimertinib demonstrated a statistically significant and clinically meaningful improvement in disease-free survival (DFS) in the adjuvant treatment of patients with early-stage (Stage IB, II and IIIA) epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC) after complete tumor resection with curative intent (Wu et al 2018a, Wu et al 2020).

In the primary endpoint of DFS in patients with Stage II and IIIA disease, adjuvant (after surgery) treatment with osimertinib reduced the risk of disease recurrence or death by 83% (based on a hazard ratio [HR] of 0.17; 95% confidence interval [CI] 0.12, 0.23; $p<0.0001$). DFS results in the overall trial population, Stage IB through IIIA, a key secondary endpoint, demonstrated a reduction in the risk of disease recurrence or death of 79% (based on a HR of 0.21; 95% CI 0.16, 0.28; $p<0.0001$) (astrazeneca.com/media-centre/press-releases).

At two years, 89% of all patients in the trial treated with osimertinib remained alive and disease free versus 53% on placebo.

To date, there are few, limited treatment options for patients in particular for those without the T790M mutation who progress on EGFR-TKIs, except chemotherapy or, in some countries, a combination of chemotherapy and immunotherapy for fit patients based on a recent subgroup analysis of IMpower150 study. Immunotherapy alone seems less effective in this population in comparison to other NSCLC subgroups (Reck et al 2019, Liu et al 2020).

[redacted]

The small sample size of each subgroup is a limitation of this analysis and has resulted in imbalances in mutation type, smoking history, previous TKI use, and potentially other

subgroups (Planchard et al 2019). Moreover, the T790M status was not widely available in the subjects and the patient number was too small to make conclusions. Overall, the findings of these subgroup analyses warrant further investigation. Results from current and future studies assessing the combination of chemotherapy and immunotherapy in T790M negative who are refractory to EGFR-TKIs will provide additional insights.

Two ongoing phase III trials, CheckMate722 (NCT02864251) and KEYNOTE789 (NCT03515837), are testing different immuno checkpoint inhibitors (ICIs) strategies in patients with EGFR-mutation-positive, T790M-negative NSCLC who failed treatment with a previous EGFR TKI and will help to elucidate the role of ICIs in the therapeutic strategy of these patients (Nakagawa et al 2016 , Riely et al 2018).

Platinum-based doublet chemotherapy is a global recommended standard of care as second-line treatment based on the data from the IMPRESS trial, a phase III study comparing gefitinib or placebo plus cisplatin-pemetrexed chemotherapy after progression on gefitinib therapy in patients with advanced EGFR mutation-positive NSCLC (Engelman et al 2007). Overall, the PFS (the primary endpoint) was 5.4 months in both arms, with an inferior OS in the gefitinib plus chemotherapy arm (13.4 versus 19.5 months). Among patients with T790M-negative disease detected in plasma the PFS was longer in those administered gefitinib plus chemotherapy (6.7 versus 5.4 months) while the OS was similar (21.4 versus 22.5 months) (Liao et al 2019).

Due to the few options available and modest treatment outcome, future investigation into the optimal management of T790M mutation–negative resistance is warranted.

T790M-negative NSCLC is seen as a heterogeneous group which comprises different molecular alterations identified as resistance mechanisms. Those include bypass pathway activation [e.g. MET amplification [MET-amp] and Human Epidermal growth factor Receptor 2 (HER2) amplification (HER2-amp)] downstream signaling pathways (e.g., PI3K and BRAF mutations), histological transformations [e.g., small cell and epithelial–mesenchymal transition (EMT)], but also other unknown mechanisms (Schrock et al 2016, Piotrowska et al 2018).

MET-amp is present in 5–20% of EGFR mutation-positive NSCLC patients who develop acquired resistance to EGFR-TKIs (TCGA 2014, Jia et al 2016). More than 5% of patients with EGFR mutation-positive NSCLC who progress on first-generation or second-generation EGFR TKIs, and up to 25% who progress on osimertinib, have MET amplification. Patients who harbor preexisting MET-amp before EGFR-TKI therapy may have a shorter time to progression on EGFR-TKI therapy (Guo et al 2020). MET-amp reactivates the PI3K/AKT pathway mediated by ErbB3 transactivation; inhibition of MET signaling could restore the sensitivity of lung cancer cells to gefitinib. Overexpression of hepatocyte growth factor (HGF), the ligand of MET, is also implicated in inducing resistance to EGFR-TKIs, and high serum levels of HGF is a poor prognostic factor in NSCLC patients treated with EGFR-TKIs. Both MET-amp and HGF overexpression can occur with or without T790M. Based on these findings, MET inhibitors were evaluated to overcome this resistance mechanism (Frampton et al 2015, Guo et al 2020, Awad et al 2019, Finocchiaro et al 2015).

Combination targeted therapy may overcome genomic heterogeneity of drug resistance. Combining EGFR TKI with an agent active on an alternative signaling pathway with a MET inhibitor may enhance activity in patients with acquired resistance to EGFR-TKIs, or delay the development of subsequent resistance via these alternate routes (Frampton et al 2015).

In EGFR-positive and MET-positive NSCLC, the combination of EGFR and MET TKIs was reported to provide promising results (Wolf et al 2020). The phase Ib TATTON trial, the combination of osimertinib and savolitinib in 51 EGFR-mutant NSCLC patients T790M-negative and acquired MET amplification after first- or second-generation EGFR TKI, reported a ORR of 65%; (95% CI, 50–78) and median duration of response (DoR) of 9 months. Likewise, the same combination in 69 T790M-negative and acquired MET amplified tumors after osimertinib reported an ORR of 30% (95% CI, 20–43) and DoR of 7.9 months (95% CI, 4.0–10.5) (Sequist et al 2020). In TATTON trial centrally confirmed MET positivity was defined by fluorescence in situ hybridization (FISH), with gene copy number [GCN] ≥5, or with MET-to–centromere chromosome 7 ratio ≥2. Personalized treatment with gefitinib and tepotinib was evaluated in 21 patients with EGFR-mutant, T790M-negative NSCLC with MET amplification (GCN ≥5 or MET-to–centromere chromosome 7 ratio ≥2) after progression while taking an EGFR TKI (not osimertinib), the small molecules combination improved PFS (21.2 versus 4.2 months [HR = 0.17, 90% CI: 0.05–0.57]) versus that with platinum-pemetrexed, as well as ORR (67% versus 43%) (Oxnard et al 2020, Eijkelenboom et al 2019).

1.1.2 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 monotherapy is currently approved by both Food and Drug Administration (FDA) (US) and The Pharmaceuticals and Medical Devices Agency PMDA (Japan) for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping mutation.

1.1.2.1 Non-clinical experience

Capmatinib has potent inhibitory activity against the MET kinase *in vitro* [inhibitory concentration IC_{50} = 0.6 nM in a biochemical assay], and is highly specific for MET with approximately 1,000-fold or greater selectivity over more than 400 other human kinases or mutant variants thereof (Baltschukat et al 2019). Potent inhibitory activity has also been observed in cell-based assays that measure MET-mediated signal transduction, as well as MET-dependent cell proliferation, survival, and migration.

In MET–dependent, mouse tumor models (including lung cancer models), capmatinib exhibits dose-dependent antitumor activity and causes tumor regression at well-tolerated doses that exceeded IC90 coverage (Liu et al 2011). Importantly, plasma levels of capmatinib correlate with both the dose administered and the extent of tumor growth inhibition in vivo. In MET/HGF-driven tumor models grown as xenografts in mice, oral dosing of capmatinib demonstrated significant in vivo activity in blocking both MET phosphorylation and tumor growth. Activation of MET in such responsive models is either due to strong MET overexpression (mostly because of gene amplification, e.g., in gastric or hepatocellular

carcinoma) or HGF secretion resulting in an autocrine loop (e.g., in glioblastoma) (Ha et al 2013).

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

1.1.2.2 Clinical experience

Capmatinib has been extensively tested in both healthy volunteers and cancer patients. As of the safety cut-off date of 28-Sep-2020, more than 780 participants with solid tumors have been treated with capmatinib as a single agent, and more than 690 participants have received capmatinib in combination with other therapies. The recommended phase II dose (RP2D) for capmatinib as a single agent has been determined to be 400 mg b.i.d. in tablet formulation [capmatinib Investigator's Brochure]. The most frequent AEs suspected to be related to capmatinib of any grade reported in study [CINC280A2201], reference study for the safety profile of capmatinib monotherapy (n=334), across study cohorts and irrespective of MET mutational status, were edema peripheral (41.6%), nausea (33.2%), blood creatinine increased (19.5%), vomiting (18.9%), fatigue (13.8%), decreased appetite (12.6%) and diarrhea (11.4%), and the majority were Grade 1/2. The Grade 3/4 AEs suspected to be related to capmatinib in the [CINC280A2201] study included edema peripheral (7.5%) and lipase increased (5.1%), alanine aminotransferase increased (4.8%), amylase increased (3.0%), fatigue (3.0%), aspartate aminotransferase increased (2.4%), nausea and vomiting (1.8%), decreased appetite (0.9%), constipation (0.6%), and diarrhea (0.3%) [capmatinib Investigator's Brochure].

Preliminary efficacy data for capmatinib single agent in MET-dysregulated NSCLC have been reported in the phase 1 study [CINC280X2102]: as of 17 July 2017, confirmed partial responses were observed in 11/55 (ORR 20%) evaluable NSCLC patients (defined as those with at least one post-baseline tumor assessment or have discontinued treatment at the time of the data cut-off) enrolled in the expansion phase (treated at the RP2D of 400 mg b.i.d. tablet or 600 mg b.i.d. capsule) and DCR was 51%. In evaluable patients with MET overexpression (Immunohistochemistry IHC 3+), confirmed partial responses were seen in 9/37 patients (ORR 24%), and the DCR was 62%. In evaluable patients with MET amplification GCN $\geq$ 6, confirmed partial responses were seen in 7/15 patients (ORR 47%), and the DCR was 80%. Kaplan–Meier median PFS was 3.7months (95% CI 1.8–7.3) in the total NSCLC population while in patients with MET GCN $\geq$ 6 median, PFS was extended to 9.3 months (95% CI 3.8–11.9). Four NSCLC patients with MET mutations were identified by retrospective Next Generation Sequencing (NGS) analysis: all 4 were IHC3+ and 3/4 had high GCN (GCN $\geq$ 10) while GCN was missing in 1 patient. Confirmed Partial Response (PR) was achieved in 3 patients while one achieved unconfirmed PR (Schuler et al 2020). Moreover, in the ongoing, multicohort, phase 2 GEOMETRY mono-1 study, Capmatinib has demonstrated activity in the subset of patients with advanced NSCLC who were either pretreated with 1 or 2 prior lines of systemic therapy (cohort 1a) with high-level MET amplified (GCN $\geq$ 10) NSCLC. ORR was 29%, median DOR was 8.31 months (20 responders, 95% CI: 4.17–15.44) (Wolf et al 2020).

Efficacy data for capmatinib single agent in previously treated patients with locally advanced or metastatic NSCLC harboring MET 14 exon skipping mutation have been reported in the group 4 of phase II GEOMETRY 1 study [CINC280A2201]: as of 15-Apr-2019, Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 confirmed major responses (including a

complete response [CR]) evaluated by BIRC were observed in 28 out of 69 (ORR 40.6%, [95% CI, 28.9-53.1]) evaluable patients (defined as those with at least one post-baseline tumor assessment or have discontinued treatment at the time of the data cut-off) and median DOR was 9.72 months [95% CI 5.55-12.98]. Median progression-free survival (mPFS) was 5.42 months [95% CI 4.17 - 6.97]. Moreover, intracranial responses were observed in 7 out of 13 evaluable patients with brain metastases at baseline. Four patients had complete resolution of lesion (Wolf et al 2019). Based on these data, capmatinib received breakthrough therapy designation for treatment of treatment-naive and pre-treated NSCLC patients with METΔex14 mutations from the US Food and Drug Administration (FDA) and was approved by FDA on 06-May-2020 for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test.

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

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

Capmatinib is a moderate Cytochrome P450 Enzymes CYP1A2 inhibitor [CINC280A2103]. Therefore, CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions should be avoided. If coadministration is unavoidable, decrease the dosage of CYP1A2 substrates in accordance with the approved prescribing information.

Capmatinib is an inhibitor of P-glycoprotein (P-gp) and BCRP (Breast Cancer Resistance Protein) transporter [CINC280A2105]. Coadminstration of capmatinib increased P-gp substrate (digoxin) exposure (AUC_{inf} and C_{max} by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUC_{inf} and C_{max} by 108% and 204%, respectively), indicating that capmatinib could potentially cause clinically relevant drug-drug interaction (DDI) with P-gp and BCRP substrates. For further details, please refer to the latest version of the [capmatinib Investigator's Brochure].

When coadministered with the strong CYP3A inhibitor itraconazole, capmatinib AUC (Area under curve) increased by approximately 40% without any change in Cmax. When coadministered with the strong CYP3A inducer rifampicin, capmatinib AUC and C_{max} decreased by 67% and 56%, respectively [CINC280A2102]. Hence, adverse reactions during coadministration of capmatinib with strong CYP3A inhibitors should be closely monitored. In addition, strong CYP3A inducers should be avoided in participants treated with capmatinib. For further details, please refer to the latest version of the [capmatinib Investigator's Brochure].

1.1.3 Overview of osimertinib

Osimertinib is a potent irreversible inhibitor of both the single EGFR mutation-positive (TKI sensitivity conferring mutation) and dual EGFR mutation-positive / T790M+ (TKI resistance conferring mutation) receptor forms of EGFR with a significant selectivity margin over wild-type EGFR (NCCN 2021). Osimertinib is approved as first-line treatment for patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an approved test, based on FLAURA trial data that demonstrated a significant improvement in PFS compared to EGFR TKI comparator (gefitinib or erlotinib) with median 18.9 months and 10.2 months, respectively, HR=0.46, 95% CI: 0.37, 0.57; P<0.001 (Soria et al 2018). On the basis of positive results of the AURA3 clinical trial, osimertinib is approved also for the treatment of patients with metastatic T790M-positive NSCLC who have previously progressed during or after EGFR-TKI therapy (Jänne et al 2015). In patients harbouring the T790M-mutation after progressing on a first or second-generation EGFR-TKI, osimertinib was superior to platinum doublet chemotherapy with a higher response rate (71% vs 31%) and longer progression free survival (10.1 vs 4.4 months, p<0.001). The median overall survival was 26.8 vs 22.5 months, p = 0.277. It has been shown that despite the absence of T790M some activity of osimertinib still is maintained in this population. In a phase I study which, in addition to T790M-positive patients, also included 50 EGFR-TKI pre-treated patients without the T790M-mutation, the latter group demonstrated an overall response rate of 28% with 10.7 months duration of response and a median PFS of 5.1 months. Previous studies in which osimertinib was given as a second-line treatment have shown superior efficacy in the CNS as compared with platinum chemotherapy (Ramalingam et al 2020). For further information, please refer to local label and prescribing information.

1.1.4 Capmatinib in combination with EGFR TKI non clinical and clinical experience

Preclinical studies of capmatinib in combination with other kinase inhibitors demonstrated its activity to overcome MET-driven resistance. In study [CINC280X2202], a phase Ib/II study enrolled EGFR-TKI pretreated, T790M-negative patients to receive gefitinib and capmatinib combination therapy, 100 patients received gefitinib (250 mg daily) and capmatinib (400 mg twice per day), with ORRs in patients with MET-amp [gene copy number (GCN) ≥ 6, n = 36] and MET overexpression (IHC 3+, n = 78) of 47% and 32%, respectively (Wu et al 2018b). MET detection by fluorescence in situ hybridization (FISH) using a cutoff value of GCN ≥ 6 may identify the group of patients who may best benefit from this treatment. Study [CINC280X2105C] combines nazartinib (EGF816, a third-generation EGFR-TKI) and capmatinib in EGFR mutation-positive NSCLC patients in various treatment settings and T790M/MET status (MET+ defined as IHC 3+ and/or gene copy number ≥ 4) (Felip et al 2020). As of 05-Feb-2019, 68 EGFR TKI first and second generation pretreated patients (2^{nd}-4^{th} line after 1^{st}/2^{nd} generation EGFR TKI) were enrolled in group Group 1 + Ph 1b RP2D (66 had known MET status, 23 MET+). An ORR of 43.5% [95% CI 23.2, 65.5] and 27.9% [95% CI 15.3, 43.7] was reported in the MET+ and MET- group respectively. PFS of 7.7 months [95% CI 5.4, 12.2] and 5.4 months [95% CI 3.5, 6.4] were reported in the MET+ and MET- group respectively, confirming the role of selective MET inhibition in this selected subset of post EGFR TKI pts. The AEs profile confirmed the good tolerability of the combination: most

frequent (≥ 30%) any-grade treatment-related adverse events were peripheral edema (50%, 57.4%), nausea (42.3%, 48.9%) and diarrhea (23.1%, 46.8%).

The clinical use of capmatinib in combination with osimertinib has been reported within capmatinib patient named program. We report a case of a patient NSCLC stage IV with brain metastases MET amplified previously progressed to different treatments: erlotinib, osimertinib (despite dose increased to 160 mg), chemotherapy with carboplatin and pemetrexed, atezolizumab, crizotinib. Patient started capmatinib 400 mg b.i.d. as single agent. When brain metastases progressed, osimertinib 160 mg was added to capmatinib, leading to rapid clinical improvement and radiological response (Gautschi et al 2020, Rusthoven and Doebele 2016, Schuette 2004, Zhang et al 2015, Shin et al 2014).

1.2 Purpose

The purpose of this prospective, randomized, controlled, open-label, multicenter, global phase III study is to evaluate the efficacy and safety of capmatinib in combination with osimertinib compared to platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy as second line treatment in patients with locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del), T790M negative, MET amplified who have progressed following either 1st/2nd generation EGFR TKIs, osimertinib or other 3rd generation EGFR TKIs used per local standard of care. The rationale for investigating the anti-cancer activity of capmatinib in combination with osimertinib in this population is as follows:

- MET amplification is the leading mechanism of resistance to EGFR TKI in EGFRm NSCLC (irrespective of the type of prior EGFR TKI) and is the basis for patient selection in the post-EGFR TKI setting. No targeted therapy against MET amplification is currently approved.
- The target population represents a high unmet medical need since to date few options with limited benefit are available for the treatment of those patients, in particular in the T790M negative setting.
- Proof of concept for capmatinib in combination with EGFR TKIs in MET positive EGFR mutated post-EGFR TKI NSCLC setting has been demonstrated with both first-generation EGFR TKI (gefitinib) and 3rd generation EGFR TKI (EGF816).

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint(s) for primary objective(s)**
Run-in part	***Run-in part***
• To confirm the recommended dose of capmatinib in combination with osimertinib for Part 2	• Incidence of Dose Limiting Toxicities (DLT) during the first 21 days (3 weeks) of treatment for each dose level associated with administration of capmatinib in combination with osimertinib
Randomized part	***Randomized part***

Objective(s)	**Endpoint(s)**
• To compare the progression free survival (PFS) of capmatinib in combination with osimertinib as compared to platinum-pemetrexed based doublet chemotherapy	• Progression free survival (PFS) per Blinded Independent Review Committee (BIRC) according to RECIST 1.1. See Section 2.1 for Primary Estimands
Key secondary objective(s)	**Endpoint(s) for key secondary objective(s)**
Randomized part	***Randomized part***
• To compare the overall response rate (ORR) of capmatinib in combination with osimertinib as compared to platinum-pemetrexed based doublet chemotherapy	• ORR calculated per RECIST 1.1 by BIRC. See Section 2.2 for Secondary Estimands
• To compare the overall intracranial response rate (OIRR) of capmatinib in combination with osimertinib as compared to platinum-pemetrexed in participants with Central Nervous System (CNS) lesions	• OIRR by BIRC as per RANO-BM criteria. See Section 2.2 for Secondary Estimands
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
Run-in part	***Run-in part***
• To characterize the safety and tolerability of capmatinib in combination with osimertinib	• **Safety**: Incidence, type, and severity of adverse events per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 including changes in laboratory values, vital signs, liver assessments and cardiac assessments; **Tolerability**: dose interruptions, reductions, dose intensity, and duration of exposure for all drug components
• To characterize the pharmacokinetics of capmatinib, osimertinib, and osimertinib's active metabolites (AZ5104 and AZ7550) in combination setting	• Plasma PK concentrations and derived PK parameters
• To assess the tumor response of capmatinib in combination with osimertinib	• All calculated per RECIST 1.1 by investigator: Overall response rate (ORR), Duration of response (DOR), Time to response (TTR), Disease control rate (DCR), Progression free survival (PFS)
Randomized part	***Randomized part***
• To assess the anti-tumor activities of capmatinib in combination with osimertinib as compared to platinum-pemetrexed	• All calculated by BIRC per RECIST 1.1: Duration of response (DOR), Time to response (TTR), Disease control rate (DCR)
• To assess PFS2 (PFS after next line of treatment)	• PFS2 based on local investigator assessment.
• To characterize the pharmacokinetics of capmatinib, osimertinib, and osimertinib's active metabolites (AZ5104 and AZ7550) in combination setting	• Plasma PK concentrations
• To evaluate overall survival (OS) in participants treated with capmatinib in combination with osimertinib as compared to platinum-pemetrexedv based doublet chemotherapy	• Overall Survival
• To evaluate the safety profile of capmatinib in combination with osimertinib as compared to platinum-pemetrexed based doublet chemotherapy	• Incidence of adverse events and serious adverse events, change in vital signs, laboratory results and ECG

Objective(s)	Endpoint(s)
• To assess the effect of capmatinib in combination with osimertinib as compared to platinum-pemetrexed on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL)	• Change from baseline in European Organization for Research and Treatment of Cancer (EORTC) QLQ-LC13, QLQ-C30, EuroQoL-5 Dimension-5 Level/EQ-5D-5L and NCCN Fact Brain Symptom index questionnaires and time to symptom deterioration for EORTC QLQ-C30, QLQ-LC13 and NCCN FBrSI questionnaires
• To assess intracranial anti-tumor activity of capmatinib in combination with osimertinib as compared to platinum-pemetrexed in participants with Central Nervous System (CNS) lesions at baseline by BIRC	• Duration of intracranial response (DOIR), time to intracranial response (TTIR), intracranial disease control rate (IDCR) by BIRC as per RANO-BM criteria
[redacted]	

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

Part 1 - Run-in part

Not applicable

Part 2 - Randomized part

The primary estimand for the randomized part is defined as below.

The primary scientific question of interest is to estimate the treatment effect based on the primary endpoint of PFS for the combination of capmatinib and osimertinib compared to platinum – pemetrexed based doublet chemotherapy for the target population, prior to receiving any post-treatment anti-neoplastic therapies.

The justification for targeting this treatment effect is that it will enable us to understand the treatment effect of capmatinib and osimertinib relative to platinum – pemetrexed based doublet chemotherapy in the absence of potentially confounding effect of any post-treatment anti-neoplastic therapy that is not part of the assigned treatment strategy.

The primary estimand is characterized by the following attributes:

1. Population: all randomized patients with locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC with EGFR activating mutation (i.e., L858R and/or ex19del), T790M negative, MET amplified who have progressed following 1st/2nd generation EGFR TKIs, osimertinib, or other 3rd generation EGFR TKIs used per local standard of care treatment. Further details on the population are provided in Section 5.
2. Treatment: randomized treatment (capmatinib in combination with osimertinib versus platinum – pemetrexed based doublet chemotherapy). Further details about the treatment are provided in Section 6.
3. Variable: progression free survival (PFS) defined as the time from the date of randomization to the date of the first documented disease progression based on BIRC as per RECIST 1.1 or date of death due to any cause, whichever occurs first.
4. Handling of remaining intercurrent events:
5. Initiation of post-treatment anti- neoplastic therapy before PFS event: PFS events that occur after the start of a new post-treatment anti-neoplastic will be censored at the last assessment prior to initiation of the new post-treatment anti-neoplastic therapy (hypothetical policy strategy)
6. Discontinuation of study treatment for any reason before PFS event:
7. PFS will take into account all PFS events irrespective of the study treatment discontinuation reasons (treatment policy strategy)
8. Any Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster: PFS will take into account all PFS events irrespective of any public health emergency (treatment policy strategy)
9. Summary measure: hazard ratio (HR) for PFS between the two treatment arms. It will be estimated using Cox proportional hazard model stratified by the randomization stratification factors. PFS will be tested using the log-rank test stratified by the randomization stratification factors.

Details on how to handle the intercurrent events are provided in Section 12.4.3.

2.2 Secondary estimands

Part 1- Run-in part

Not applicable.

Part 2- Randomized part

The following two key secondary estimands for efficacy are considered for the randomized part.

I.The first key secondary estimand is to estimate the treatment effect of the combination of capmatinib and osimertinib compared to platinum – pemetrexed based doublet chemotherapy based on ORR for the target population regardless of discontinuation of treatments and any unforeseen Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, refer to Section 4.6. The estimand is defined by the following attributes:

1) The population is all randomized patients with locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC with EGFR activating mutation (ie., L858R and/or ex19del), T790M negative, MET amplified who have progressed following 1st/2nd generation EGFR TKIs, osimertinib, or other 3rd generation EGFR TKIs used per local standard of care treatment.

2) The treatment attribute is randomized treatment (capmatinib in combination with osimertinib versus platinum – pemetrexed based doublet chemotherapy).

3) The variable is best overall response (BOR) defined as the best response recorded from the date of randomization until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started) based on BIRC per RECIST 1.1 with responses after the use of new anti-cancer therapy considered as non-response.

4) The summary measure is the difference in ORR (defined as the proportion of participants with confirmed best overall response (BOR) of CR or partial response (PR) based on BIRC per RECIST 1.1) of the two treatments and its 95% confidence interval from the stratified Miettinen and Nurminen's method (Miettinen and Nurminen 1985) with randomization strata weighting by sample size with a single treatment covariate.

5) The remaining intercurrent events are:

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

Discontinuation of study treatment for any reason: BOR will take into account all response assessments irrespective of the study treatment discontinuation reasons (treatment policy strategy)

Any Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, will be handled by treatment policy strategy.

II.The second key secondary estimand is to estimate the treatment effect of the combination of capmatinib and osimertinib compared to platinum – pemetrexed based doublet chemotherapy based on OIRR for the target population with baseline brain metastasis as per RANO-BM criteria regardless of discontinuation of treatments and any unforeseen Public Health emergency

as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster. The estimand is defined by the following attributes:

1) The population is as the subgroup of all randomized participants with locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC with EGFR activating mutation (i.e., L858R and/or ex19del), T790M negative, MET amplified who have progressed following1st/2nd generation EGFR TKIs, osimertinib or other 3rd generation EGFR TKIs used per local standard of care treatment and with baseline brain metastasis as per RANO-BM criteria.

2) The treatment attribute is randomized treatment (capmatinib in combination with osimertinib or platinum – pemetrexed based doublet chemotherapy).

3) The variable is the best overall intracranial response (BOIR) recorded from the date of randomization until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started) based on BIRC per RANO-BM with responses after the use of new anti-cancer therapy considered as non-response.

4) The summary measure is the difference in OIRR (defined as the proportion of participants with confirmed best overall intracranial response (BOIR) of CR or partial response (PR) based on BIRC per RANO-BM) of the two treatments and its 95% confidence interval from the stratified Miettinen and Nurminen's method (Miettinen and Nurminen 1985) with randomization strata weighting by sample size with a single treatment covariate.

5) The remaining intercurrent events are:

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

Discontinuation of study treatment for any reason: BOIR will take into account all response assessments irrespective of the study treatment discontinuation reasons (treatment policy)

Any Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, will be handled by treatment policy strategy.

3 Study design

This is a multicenter, open-label, randomized, controlled, global phase III study that will enroll adult participants with locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC with EGFR activating mutation (i.e., L858R and/or ex19del), T790M negative, MET amplified who have progressed following 1st/2nd generation EGFR TKIs, osimertinib or other 3rd generation EGFR TKI used per local standard of care treatment. Randomization of participants who have progressed on prior line with osimertinib will be a minimum of 50% of the planned total number of participants while patients who progressed on other 3rd generation EGFR TKI will represent a maximum of 10% of the planned total number of participants. The study will consist of an initial run-in part to evaluate the safety and tolerability of capmatinib in combination with osimertinib and to confirm the recommended dose for the randomized part, and a randomized part that will evaluate the efficacy and safety of capmatinib in combination with osimertinib compared to platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy as second line treatment.

The study will enroll approximately 10 to 20 participants in the run-in part and approximately 225 participants in the randomized part.

Run-in part:

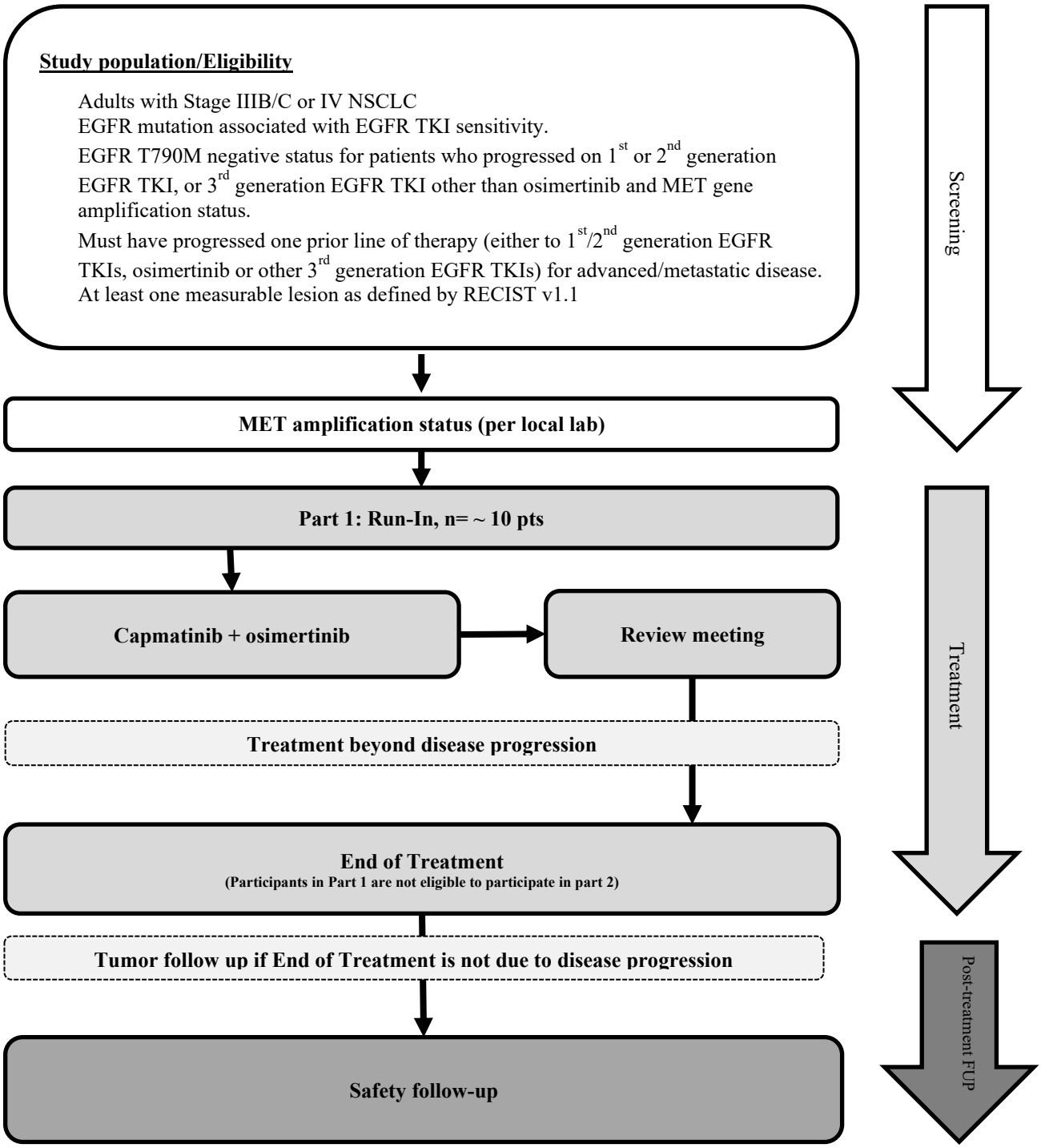
Approximately 10 participants will be enrolled and treated with dose level 1 (DL1) of 400 mg b.i.d. of capmatinib in combination with 80 mg q.d. of osimertinib, in order to have at least 6 evaluable participants during the Dose Limiting Toxicity (DLT) period (DLT period defined as the first cycle - 1 cycle = 21 days).

A review meeting to evaluate the safety and tolerability of the DL1 will take place after the sixth evaluable participant has been treated for at least 21 days. If DL1 is tolerated, capmatinib 400 mg b.i.d. in combination with osimertinib 80 mg q.d will be the recommended dose for the randomized part.

If DL1 is not tolerated, a second cohort of approximately 10 participants may be added to have at least 6 evaluable patients. This second cohort will be treated at a lower dose level (DL-1) of 400 mg b.i.d. capmatinib in combination with 40 mg q.d. osimertinib. The same rule utilized for the evaluation of DL1 will be utilized to evaluate DL-1. A dose level review team meeting will take place after the sixth evaluable participant of that second cohort has been treated for at least 21 days. If DL-1 is tolerated, capmatinib 400 mg b.i.d. in combination with osimertinib 40 mg q.d will be the recommended dose for the randomized part. If DL-1 is not tolerated, the randomized part will not open. See also Section 6.5.1.

Participants participating in the run-in part are not eligible to participate in the randomized part.

Figure 3-1 Part 1: Run-in Part



Randomized Part:

In the randomized part, approximately 225 participants will be randomized in a 2:1 ratio to either capmatinib plus osimertinib (n≈150) or to platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy (n≈75).

Participants will be stratified based on the following factors:

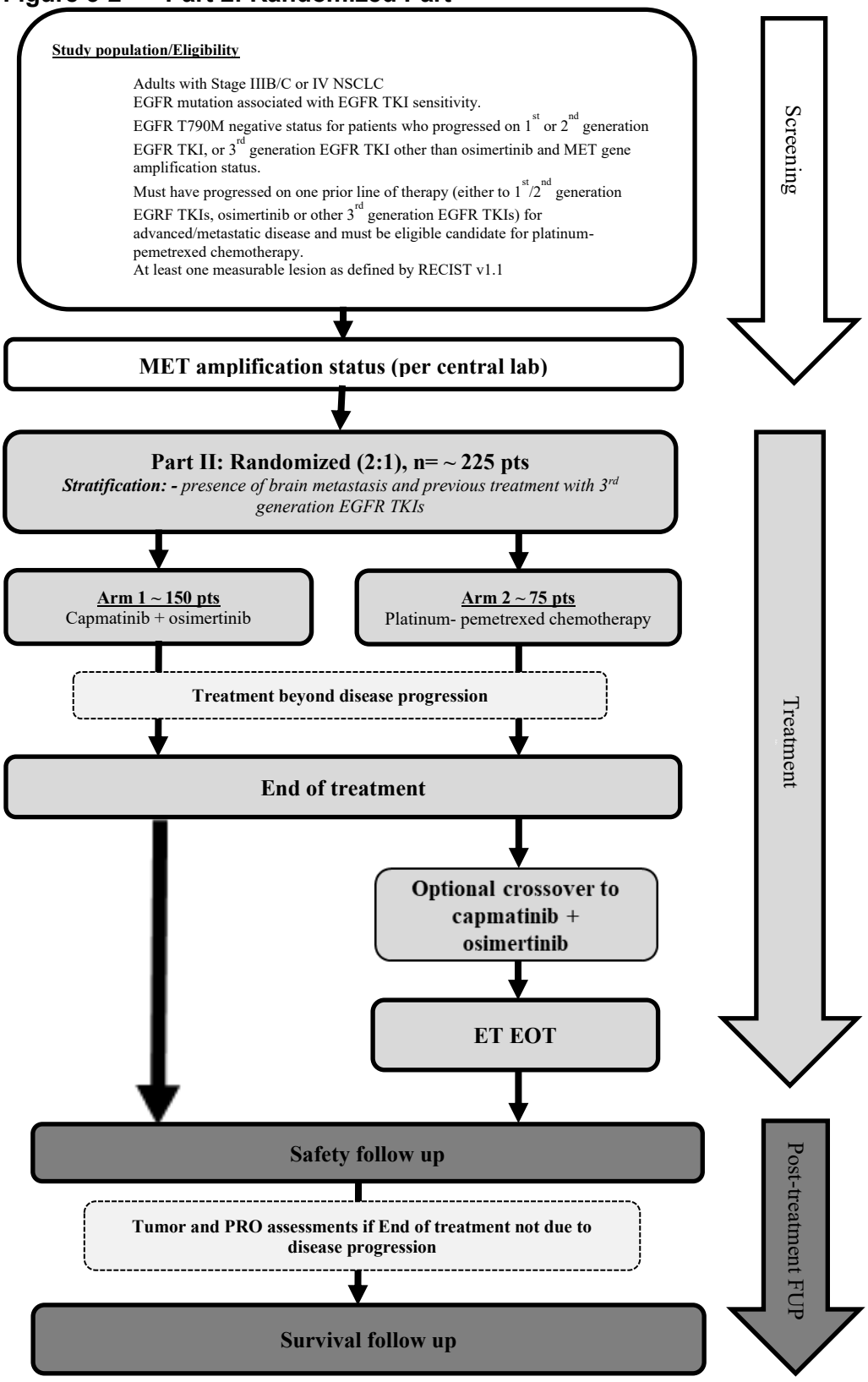
- Presence of brain metastasis (yes/no)
- Previous treatment with 3rd generation EGFR TKIs (yes/no)

Randomization of participants who progressed on prior line with osimertinib will be a minimum of 50% of the planned total number of participants while patients who progressed on other third generation EGFR TKI will represent a maximum of 10% of the planned total number of participants.

An independent Data Monitoring Committee (DMC) will be monitoring the safety of the participants on a regular basis.

Participants randomized to platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy treatment will be allowed to crossover to receive study treatment (capmatinib in combination with osimertinib) after blinded independent review committee (BIRC) confirmed, RECIST 1.1-defined progressive disease (PD) and after meeting the eligibility criteria outlined in Section 6.1.5.2.

Figure 3-2 Part 2: Randomized Part



Pre-Screening

In order to be considered eligible for the study, participants must have written documentation of an EGFR activating mutation and, for patients who have progressed on 1st or 2nd generation EGFR TKIs, or 3rd generation EGFR TKI other than osimertinib, also EGFR T790M negative result by tissue. Participants previously treated with osimertinib are not required to have confirmation of EGFR T790M negative tumor status however those with known T790M positive tumor status are excluded from the study.

The results from procedures performed as part of the local standard practices (prior to enrolling in the trial) will satisfy the inclusion criteria. Additionally, eligible participants must have MET amplification per local results in tissue or blood for the run-in part or as confirmed in tissue by a Novartis designated central laboratory for the randomized part. Participants must sign a molecular pre-screening Informed Consent Form (ICF) prior to any study specific molecular pre-screening evaluations. Refer to Section 8.1 for additional details.

Screening and Randomization

Participants must sign the main Informed Consent Form (ICF) prior to any study specific screening evaluations.

For the randomized part only: following completion of all required screening procedures (refer to Section 8.1 and Section 8.2) and verifying participant eligibility, the participant will be randomized via the Interactive Response Technology (IRT) system.

Treatment

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

Participants will be evaluated radiologically at screening/baseline then every 6 weeks for the first 18 months after C1D1, then every 12 weeks (+/- 7 days), to assess treatment response until PD by RECIST 1.1 (as assessed by the investigator in the run-in part, and as assessed by the investigator confirmed by BIRC in the randomization part)

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

Participants randomized to the platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy arm will be allowed to crossover to receive capmatinib in combination with osimertinib therapy after BIRC-confirmed RECIST 1.1-defined PD, and after meeting eligibility criteria outlined in Section 6.1.5.2. Such participants must complete the EOT visit after permanent discontinuation of platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy. The subsequent ET-EOT visit will be performed for participants who crossover when they permanently discontinue treatment with capmatinib in combination with osimertinib.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents the conduct of on-site study visits, special effort should be made for the EOT and ET-EOT visits. If it is not

feasible to conduct the EOT and ET-EOT visits on-site, virtual visits or visits to the participant´s home should be attempted.

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

After treatment discontinuation from the capmatinib + osimertinib arm, all participants will be followed for safety evaluations as outlined in detail in Section 6.5.5 and Section 9.2 during the safety follow-up period. After treatment discontinuation from platinum – pemetrexed chemotherapy arm due to PD (confirmed by BIRC), participants are allowed to crossover to capmatinib + osimertinib therapy if the criteria in Section 6.1.5.2 are met. In this case, the safety follow-up will only occur after discontinuation from ET.

Participants will be followed for safety up to 30 days after the last dose of study treatment. If a new antineoplastic therapy is initiated after study treatment, safety follow-up will focus on events suspected to be related to study treatment only.

In addition to the 30-day safety follow-up, participants who discontinue study treatment without prior documented PD, will continue efficacy assessments (Efficacy Follow-up) during the post-treatment follow-up, irrespective of start of new anti-neoplastic therapy and until documented PD by RECIST 1.1 (as assessed by the investigator in the run-in part, and as assessed by the investigator confirmed by BIRC in the randomization part), participant withdrawal of consent, physician's decision, lost to follow-up, death or if study is terminated by the sponsor as outlined in Section 9. For all participants of Part 2 (randomization), patients -reported outcomes will also continue to be collected (PRO Follow-up) until documented progression, and at three time points following to progression (refer to Section 8.5.1).

Survival Follow-up (only for randomized part)

All participants of randomized part will be followed for survival once they discontinue study treatment and tumor evaluations. Survival follow-up for participants who crossed over to capmatinib + osimertinib therapy will only occur after discontinuation from ET. The participant’s survival status will be collected every 12 weeks as part of the survival follow-up phase.

For all participants (either in the run-in or randomized part):

Participant's respective study treatment (either with capmatinib in combination with osimertinib, or with platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy) will be continued until participant experiences any of the following: documented disease progression by RECIST 1.1 (as assessed by the investigator in the run-in part, and as assessed by the investigator confirmed by BIRC in the randomization part), withdrawal of consent, pregnancy, lost to follow-up, or death (please refer to Section 9). Study treatment may be continued beyond initial disease progression as per RECIST 1.1 (as assessed by the investigator in the run-in part, and as assessed by the investigator confirmed by BIRC in the randomization part), if, in the judgement of the investigator, there is evidence of clinical benefit, and the participant wishes to continue on the study treatment (for additional details please refer to Section 6.1.5.1).

After treatment discontinuation, all participants will be followed for safety evaluations during the safety follow-up period.

Participants who discontinued study treatment for reasons other than disease progression, death, lost to follow-up, or withdrawal of consent will enter in a post-treatment efficacy follow-up.

Only in the randomized part, the participant's survival status will be collected every 12 weeks as part of the survival follow-up (for additional details please refer to Section 9).

For participants who crossed over to capmatinib + osimertinib therapy, safety and survival follow-ups will only occur after discontinuation from ET.

4 Rationale

The rationale for investigating the anti-cancer activity of capmatinib in combination with osimertinib is due to the unmet medical need and lack of a current targeted approved therapy for the MET amplification that is one of the leading mechanisms of resistance to EGFR TKI in EGFR mutated NSCLC. Few options to date are available for this population with limited benefit, in particular in the EGFR T790M negative setting.

Proof of concept for capmatinib in combination with EGFR TKIs in MET positive EGFR mutated post-EGFR TKI NSCLC setting has been demonstrated with both first-generation EGFR TKI (gefitinib) and 3rd generation EGFR TKI (EGF816).

4.1 Rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Study population	The study will enroll adult participants with locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC with EGFR activating mutation (i.e., L858R and/or ex19del), T790M negative, MET amplified who have progressed following EGFR TKIs either 1st and 2nd generation EGFR TKI, osimertinib or other 3rd generation EGFR TKIs used per local standard of care. Randomization 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. Refer to Section 1.1.1.
Randomization (strata, allocation ratio)	Participants will be randomized with a 2:1 ratio, as the efficacy of standard chemotherapy in this setting is currently poor. Therefore, the randomization 2:1 increases the chances for participants to receive a targeted therapy capmatinib in combination with osimertinib, given promising activity observed with the combination of capmatinib and other EGFR inhibitors (gefitinib and EGF816) as well as other MET inhibitors with osimertinib.Presence of brain metastasis at baseline (presence vs absence) and previous treatment with 3rd generation EGFR TKIs (yes vs no) were chosen as stratification factors due the expected difference in clinical outcome between participants based on this strata.
Open label	The trial is open-label for the following reasons: 1) Double blind would require i.v. placebo administration in the capmatinib/osimertinib arm, which would pose an unnecessary burden for the patient, 2) difference in premedication requirements between the two arms, which would pose also an unnecessary burden for the participants and 3) varying toxicities between the study treatments.

Study Design Aspect	Rationale
Treatment beyond progression	This is to ensure those participants (in either arm) who have disease progression per RECIST 1.1 as determined by investigator (run-in part) and as determined by investigator and confirmed by BIRC (randomized part) to continue the combination of capmatinib + osimertinib treatment, as long as they are clinically stable, tolerate the treatment, and are deriving clinical benefit according to investigator judgement. Timely follow-up after the initial PD will ensure that participants with confirmed/rapid progression will be discontinued and can initiate alternative therapies.
Crossover	The possibility to crossover increases the chances for participants treated with platinum - pemetrexed based doublet chemotherapy to receive capmatinib in combination with osimertinib which has shown preliminary meaningful clinical activity in this population of MET amplified NSCLC.

4.2 Rationale for dose/regimen and duration of treatment

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

The recommended dose for osimertinib monotherapy is 80 mg once a day until disease progression or unacceptable toxicity. Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose should be reduced to 40 mg taken once daily. For further information on posology and methods of administration please refer to the current local prescribing information for osimertinib in this disease setting.

The capmatinib 400 mg b.i.d. and osimertinib 80 mg q.d. were selected as the doses for this combination and are justified based on evaluation of potential overlapping toxicities and pharmacokinetic drug interactions.

Regarding drug-drug interaction (DDI) potential, no CYP related DDI is anticipated between capmatinib and osimertinib, but transporter related DDI is possible. Capmatinib is a P-gp and BCRP inhibitor. Osimertinib and its active metabolites (AZ5104 and AZ7550) are the substrates of P-gp and BCRP, therefore, their exposure may be increased when coadministered with capmatinib. However, during the dose finding part of the first in Human (FiH) study (AURA study, D5160C00001), osimertinib was evaluated with increasing dose levels up to 240 mg (3 times the recommended dose). The Maximum Tolerated Dose (MTD) was not reached and no apparent dose-efficacy relationship was demonstrated over the dose range of 20 mg to 240 mg. The exposure of capmatinib is not expected to be affected by osimertinib (Jänne et al 2015).

In this study, treatment will continue until disease progression or other reasons for drug discontinuation. Treatment with capmatinib in combination with osimertinib may be continued beyond RECIST 1.1-defined PD (as assessed by the investigator in the run-in part; and as assessed by the investigator and confirmed by BIRC for the randomized part) if considered by the investigator to be in the best interest of the participant and as long as no new anticancer treatment is initiated.

Treatment beyond progression with capmatinib alone or osimertinib alone is not permitted.

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

There are no current effective recommended targeted therapies for NSCLC patients with acquired EGFR-TKI resistance who are T790M negative. Pemetrexed in combination with cisplatin is approved worldwide for the treatment of advanced non squamous NSCLC and is recognized as a standard of care demonstrating superior OS compared to gemcitabine in combination with cisplatin in previously untreated advanced NSCLC patients with non-squamous histology (adenocarcinoma and large cell carcinoma) in a randomised phase III trial: 12.6 vs 10.9 and 10.4 vs 6.7 months respectively (Scagliotti et al 2008). Treatment guidelines for 2nd line treatment of EGFR mutation-positive, T790M negative NSCLC include using platinum based chemotherapy doublet treatment based on the data from the IMPRESS trial (Liao et al 2019) (for IMPRESS trial results please refer to Section 1.1).

Results of the IMpower 150 trial (for the results please refer to Section 1.1), which included data on patients with EGFR or ALK genetic alterations who failed prior targeted therapy, could support the use of a combination of atezolizumab (anti-PD-L1) and bevacizumab with carboplatin and paclitaxel (ABPC) as a therapeutic option in fitting patients with non-squamous NSCLC, and a PS of 0–1, in the absence of contraindications to the use of immunotherapy and may be an option also in the second-line setting. However, this treatment is not available worldwide for the treatment of EGFR mutated NSCLC, particularly in Asian countries where most of the participants are expected to be recruited.

Therefore, pemetrexed in combination with either cisplatin or carboplatin is an appropriate control arm treatment in this phase III trial.

4.4 Purpose and timing of interim analyses

To reduce the participant's exposure to potentially non-efficacious treatment, an interim analysis (IA) for futility is planned for PFS in this study when approximately 65 events have occurred (40% of total PFS events) at approximately 18.5 months from the date of first participant randomized in the randomized part of the study. Approximately 130 participants (57.8%) are expected to have been enrolled/randomized at the time of interim analysis.

4.5 Risks and benefits

The participants enrolled in this study will have stage IIIB/IIIC or stage IV NSCLC with EGFR activating mutation (i.e., L858R and/or ex19del), T790M negative, MET amplified (defined as GCN $\geq$ 5 by central Novartis laboratory) who have progressed following1st/2nd generation EGFR TKIs, osimertinib or other 3rd generation EGFR TKIs used per local standard of care treatment. Given the clinical and molecular characteristics of MET amplified T790M negative NSCLC, participants have few therapeutic options with limited benefit in this study population.

The safety profile of capmatinib and osimertinib as monotherapy is well characterized (see Section 1.1.2 and Section 1.1.3). Although different studies have evaluated capmatinib in combination with different EGFR TKI inhibitors (erlotinib, gefitinib, EGF816), experience of the combination with osimertinib is limited to patient named program. Therefore, different

measures will be taken to reduce the number of participants who could be exposed to unwanted toxicity:

- A safety run-in part in a small cohort of participants is intended to allow an assessment of the safety profile of this new combination before enrolling more participants into the randomized part.
- A dose level review team composed of Novartis personnel and the investigators whose sites have enrolled participants in the safety run in part, will meet to evaluate potential DLT and for the confirmation of the recommended dose for the randomized part.
- In the randomized part, an independent Data Monitoring Committee (DMC) will be monitoring the safety of the participants on a regular basis. Unless otherwise requested by the DMC members, the first DMC will convene after the first 10 participants have been treated with the combination (capmatinib + osimertinib), as specified in the protocol and have completed the first cycle of treatment. The second meeting of the DMC will occur approximatly 3 months after the first meeting or when 90 participants are treated, whichever occurs first. Further DMC meetings will occur approximately every 6 months. DMC members will be consulted to ensure appropriate frequency.

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

The central MET amplification test used for enrollment is investigational and is being clinically validated for selecting participants most likely to benefit from capmatinib as a part of this study. Therefore, how well the test performs to identify participants who are most likely to benefit from capmatinib or to determine whether the benefits of capmatinib treatment will outweigh any potential serious side effects or risks has not been fully established. However, the test is sufficiently validated for the purposes of selecting participants with MET amplification in their NSCLC tumor sample for enrollment to this study.

The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as by close clinical monitoring and oversight and MET amplification assay monitoring. As with any clinical study, there may be unforeseen risks with the study treatment, which could be serious. The specific risks for each compound are discussed in Section 4.5.1 and Section 4.5.2. For further details, refer to the toxicity data provided in the [capmatinib Investigator's Brochure] and in the osimertinib local prescribing information.

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Therefore, the overall safety risk to participants enrolled in the study [CINC280L12301] is considered manageable, based on the available clinical safety data for both capmatinib and

osimertinib, along with the eligibility criteria and monitoring measures implemented in this study.

Given the unmet medical need in the intended patient population, the lack of well-proven treatment options, the preliminary evidence of efficacy with capmatinib in combination with EGFR TKI inhibitors in NSCLC EGFRm patient progressing on EGFR TKI (>40% ORR in MET+ population) and the well tolerated profile reported in ongoing studies [INC280X2105c] and [INC280X2202], it is considered appropriate to assess efficacy and safety of capmatinib in combination with osimertinib in a randomised open-label phase III study in 2nd line NSCLC versus pemetrexed in combination with cisplatin or carboplatin.

4.5.1 Capmatinib

Based upon the clinical experience with capmatinib to date, the overall risk-benefit assessment of capmatinib is considered favorable (see Section 1.2). The data from study [CINC280A2201] show that capmatinib is generally well tolerated and has a manageable safety profile. The safety profile in the METΔex14 mutated or MET amplified NSCLC population is consistent with the safety profile of capmatinib across multiple clinical studies.

The most frequent safety findings on treatment with capmatinib monotherapy include peripheral edema, nausea, increased blood creatinine, vomiting, fatigue, decreased appetite, and diarrhea.

In addition, pancreatic related events (e.g., amylase and lipase increase), and changes in liver blood parameters (Alanine Aminotransferase (ALT) and/or Aspartate Aminotransferase (AST) and/or bilirubin increase) have been observed in participants treated with capmatinib. To date, a direct toxic effect of capmatinib on pancreas could not be identified. Caution is recommended when capmatinib is administered in combination with other drugs with a known risk of hepatotoxicity.

Pneumonitis and Interstitial Lung Disease (ILD) have been reported from both capmatinib single agent and combination studies with EGFR TKIs, including events with fatal outcomes. Investigators are advised to carefully monitor participants for signs and symptoms of pneumonitis/ILD and implement dose modification and follow-up evaluations described in the protocol in all capmatinib studies, both single agent and in combination studies. If ILD/pneumonitis is diagnosed, capmatinib should be permanently discontinued and appropriate treatment initiated as necessary. Reintroduction of capmatinib should be considered only in the absence of a diagnosis of ILD/pneumonitis and after careful consideration of the individual participant's benefits and risks.

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

For further information on potential toxicities and Drug-Drug Interaction (DDI), please refer to the current [capmatinib Investigator's Brochure].

Assessment of the Benefit/Risk did not reveal any additional risks related to COVID-19 in participants treated with capmatinib. Based on the available data, no additional risk has been observed in participants who were administered COVID-19 vaccines while on capmatinib.

4.5.2 Osimertinib

The safety profile of osimertinib is characterized by the majority of adverse events being non-clinically significant, i.e., diarrhoea and skin rash. Below safety profile is pertaining the data from the 1142 patient recruited in FLAURA and AURA trials (Scott 2018).

[redacted]

Cardiomyopathy occurred in 2.6% of osimertinib treated patients, 0.1% of cardiomiopathy were fatal. Changes in cardiac contractility were reported across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 3.9% of patients treated with osimertinib who had baseline and at least one follow-up LVEF assessment.

Severe, life-threatening or fatal Interstitial Lung Disease (ILD) or ILD-like adverse reactions (i.e., pneumonitis) have been observed in patients treated with osimertinib in clinical studies. Most cases improved or resolved with interruption of treatment. Interstitial Lung Disease (ILD) or ILD-like adverse reactions (i.e., pneumonitis) were reported in 3.9% and were fatal in 0.4% of the patients who received osimertinib. The incidence of ILD was 10.4% in patients of Japanese ethnicity, 1.8% in patients of Asian ethnicity and 2.8% in non-Asian patients. Case reports of Stevens-Johnson syndrome (SJS) have been rarely observed in association with osimertinib treatment.

Careful assessment of all participants with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD/pneumonitis. Treatment with this medicinal product should be interrupted pending investigation of these symptoms. If ILD/pneumonitis is diagnosed, osimertinib should be permanently discontinued and appropriate treatment initiated as necessary. Reintroduction of osimertinib should be considered only in the absee of diagnosis of ILD/pneumonitis and after careful consideration of the individual participant's benefits and risks.

For further information relating the safety and tolerability of osimertinib, please refer to local approved label.

4.5.3 Cisplatin, carboplatin and pemetrexed

Pemetrexed can cause severe myelosuppression resulting in a requirement for transfusions and which may lead to neutropenic infection. The risk of myelosuppression is increased in patients who do not receive vitamin supplementation. Complete blood count be periodically monitored during treatment as required by local standard of practice. The incidence of Grade 3-4 neutropenia was 15% and 23%, the incidence of Grade 3-4 anemia was 6% and 4%, and incidence of Grade 3-4 thrombocytopenia was 4% and 5%, respectively. Pemetrexed can cause severe, and sometimes fatal, renal toxicity. The incidences of renal failure in clinical studies in which patients received pemetrexed with cisplatin were: 2.1% in renal function should be periodically monitored during treatment as required by local standard of practice.

Serious and sometimes fatal, bullous, blistering and exfoliative skin toxicity, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis can occur with pemetrexed. Serious interstitial pneumonitis, including fatal cases, can occur with pemetrexed. Carboplatin/Cisplatin produces severe cumulative nephrotoxicity.

Appropriate hydration will tend to minimize carboplatin/cisplatin nephrotoxicity, renal function should be periodically monitored during treatment as required by local prescribing information. Severe cases of neuropathies have been reported. These neuropathies may be irreversible and may manifest by paresthesia, areflexia and a proprioceptive loss and a loss of vibration perception. A loss of motor function has also been reported.

Appropriate neurological examination should be carried out at regular intervals as required by local prescribing information. Ototoxicity has been observed and is manifested by tinnitus and/or hearing loss in the high frequency range (2000 to 8000 Hz). Decreased ability to hear conversational tones may occur occasionally. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; however, deafness after initial dose of cisplatin has been reported rarely. Careful monitoring by audiometry should be performed as required by l local prescribing information. Anaphylactic-like reactions to cisplatin have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to carboplatin/cisplatin and have been alleviated by administration of adrenaline, steroids and antihistamines. Nausea and vomiting may be intense and require adequate antiemetic treatment.

Close supervision must be carried out with regard to ototoxicity, myelosuppression and anaphylactic reactions. For further information please refer to the local prescribing information.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of Public Health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

This study will enroll adult male and female participants with EGFR activating mutation (i.e., L858R and/or ex19del), T790M negative, advanced (stage IIIB, IIIC or IV) NSCLC harboring MET amplification as determined by a Novartis central molecular laboratory and who have progressed following $1^{st}/2^{nd}$ generation EGFR TKIs, osimertinib or other third generation EGFR TKIs used per local standard of care' for consistency with protocol summary.

The study will enroll approximately 10 to 20 participants in the run-in part and will enroll approximately 225 participants in the randomized part globally.

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

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study
2. Adult ≥ 18 years old at the time of informed consent (≥20 years of age in Japan)
3. Stage IIIB/IIIC (not amenable to curative surgery, chemoradiation or radiation) or stage IV NSCLC at the time of study entry (according to Version 8 of the American Joint Committee on Cancer (Chun et al 2018)
4. Participants must have a life expectancy of at least 3 months
5. Histologically or cytologically confirmed diagnosis of NSCLC (excluding squamous cell carcinoma and histological transformation from NSCLC into small cell lung cancer (SCLC) following previous EGFR TKI treatment) with all the following:
   - EGFR mutations known to be associated with EGFR TKI sensitivity. This must be assessed as part of the patient standard of care by a validated test for EGFR mutations, as per local regulations. Exon19del, 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 of the USA must be documented in the patient source documents before the patient can be consented for pre-screening for MET amplification status.
   - EGFR T790M negative status for participants who have progressed on 1st or 2nd generation EGFR TKI, or 3rd 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 patient source documents before the patient can be randomized. If a local T790M result is not available, T790M status in tissue per central Novartis-designated laboratory result is required (only applicable for participants joining randomized part).
   - MET gene amplification status, after radiological progression on prior EGFR TKI, defined as:
     - Run-in part: IHC 3+ (defined as ≥ 50% of cells staining with high intensity) and/or MET Gene Copy Number (GCN) ≥ 5 will be utilized as study entry parameters by local test in tissue or blood.
     - Randomized part: GCN≥ 5 per central Novartis-designated laboratory result from tissue sample test.
6. Mandatory provision of a formalin-fixed, paraffin embedded tumor tissue sample (a newly obtained tumor sample, or archival tumor block/slides taken after progression on prior line of EGFR TKI) in a quantity sufficient to allow the confirmation of MET amplification (and EGFR T790M if applicable) status for all participants and potential companion diagnostics development. Tumor samples must contain at least 10% tumor content.
7. Participants must have progressed on one prior line of therapy including either to 1st/2nd generation EGFR TKIs, osimertinib or other 3rd generation EGFR TKIs used per local standard of care for advanced/metastatic disease (stage IIIB/IIIC [not amenable for curative surgery, chemoradiation or radiation or stage IV NSCLC) and must be eligible candidates for platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy. 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 1st/ 2nd EGFR TKIs (e.g., erlotinib, gefitinib, afatinib, dacomitinib), osimertinib or other 3rd 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.

8. Participants must have recovered from all toxicities related to prior systemic therapy to grade ≤ 1 (CTCAE v 5.0). Exception to this criterion: participants with any grade of alopecia and vitiligo are allowed to enter the study.
9. At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.
10. Participants must have adequate organ function including the following laboratory values at the screening visit (as assessed by local laboratory for eligibility of the run-in part eligibility, and by central laboratory for eligibility of the randomized part; except for China, where local laboratory results can be used for eligibility):
    - Absolute neutrophil count (ANC) > 1.5 x 10^9/L without growth factor support
    - Platelets > 100 x 10^9/L
    - Hemoglobin (Hgb) > 9 g/dL
    - Calculated creatinine clearance (using Cockcroft-Gault formula) > 50 mL/min
    - Total bilirubin ≤ 1.5 upper limit of normal (ULN)
    - Aspartate transaminase (AST) ≤ 2.5 x ULN except for participants with liver metastasis, who may only be included if AST ≤ 5 x ULN
    - Alanine transaminase (ALT) ≤ 2.5 x ULN except for participants with liver metastasis, who may only be included if AST ≤ 5 x ULN
    - Asymptomatic serum amylase ≤ grade 2. 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
11. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
12. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

5.2 Exclusion criteria

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

1. Prior treatment with any MET inhibitor or HGF-targeting therapy.
2. Participants with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks

prior to study entry to manage CNS symptoms. If participants are on corticosteroids for endocrine deficiencies or tumor-associated symptoms other than CNS related, dose must have been stabilized (or decreasing) for at least 5 days before Cycle 1 Day 1.

3. Carcinomatous meningitis.
4. Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type. Participants with histological transformation from NSCLC into small cell lung cancer (SCLC) following previous EGFR TKI treatment are also excluded.
5. 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).
6. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome.
7. Clinically significant, uncontrolled heart diseases such as:
   - Unstable angina within 6 months prior to screening
   - Myocardial infarction within 6 months prior to screening
   - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
   - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) > 160 mm Hg and/or Diastolic Blood Pressure (DBP) > 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening. If white coat syndrome (WHS) is suspected, blood pressure measurements may be repeated.
   - Ventricular arrhythmias
   - Supraventricular and nodal arrhythmias not controlled with medication
   - Other cardiac arrhythmia not controlled with medication
   - Fridericia QT correction formula (QTcF) > 470 ms on the screening Electrocardiogram (ECG) (as mean of triplicate ECG, and assessed by central ECG)
8. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting Cycle 1 Day 1 or participants who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤ 2 weeks prior to Cycle 1 Day 1, or participants who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions or radio-surgery for isolated brain lesions ≤ 2 weeks prior to Cycle 1 Day 1 is allowed.
9. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to starting study treatment (2 weeks for resection of brain metastases), or participants who have not recovered from the side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy for biopsy purpose only will not be counted as major surgery and participants can be enrolled in the study ≥1 week after the procedure.
10. Participants receiving treatment with strong inducers of CYP3A and could not be discontinued > 1 week prior to the start of treatment.

11. Treatment with a prior 1st or 2nd generation EGFR TKIs (e.g., erlotinib, gefitinib, afatinib, dacomitinib) osimertinib or another 3rd generation EGFR TKIs such as almonertinib and furmonertinib 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).
12. 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.
13. Impairment of Gastrointestinal (GI) function or GI disease that may significantly alter the absorption of capmatinib or osimertinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
14. Unable or unwilling to swallow tablets as per dosing schedule.
15. Substance abuse, active infection or other severe, acute, or chronic medical or psychotic conditions or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results.

    Active infection is including but not limited to Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and human immunodeficiency virus (HIV). Screening for known chronic conditions is not required.

    Participants with known serologic evidence of chronic HBV or HCV infection whose disease is controlled under antiviral therapy, according to local regulation are eligible.

    Participants with known history of testing positive for human immunodeficiency virus (HIV) infection, and with a history of acquired immunoeficiency 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. 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 treatment, they should have the disease under control and suppressed viral loads defined as per local guideline. HIV participants coinfected with hepatitis virus must also be excluded.
16. Participants with known hypersensitivity or contraindications to capmatinib or osimertinib or carboplatin or pemetrexed or cisplatin, or any excipient of these agents.
17. Pregnant or nursing (lactating) women.
18. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception as precautions. Those precautions must be used during treatment with capmatinib and osimertinib and for at least 6 weeks or following osimertinib local label prescription (whichever is longer) after stopping study treatment. In case capmatinib is utilized as single agent those precaution should be followed for at least 7 days.

For platinum (cisplatin or carboplatin) – pemetrexed based doublet chemotherapy, local prescribing information relating the time limits for such precautions and any additional restrictions will be followed.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (i.e., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), or total hysterectomy at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Use of hormonal contraceptives that are not prone to drug-drug interaction (levonorgestrel intra-uterine system [IUS; Mirena], medroxyprogesterone injection [Depo-Provera] and copper-banded intra-uterine devices. All hormonal methods of contraception must be used in combination with the use of condom by the male sexual partner for intercourse. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when confirmed by follow-up hormone level assessment is considered not of child-bearing potential.

19. Sexually active males unless they use a condom during intercourse while taking capmatinib and osimertinib for at least 4 months or following osimertinib local label prescription (whichever is longer) after stopping study treatment and should not father a child in this period. In case capmatinib is utilized as single agent those precaution should be followed for at least 7 days after stopping study treatment and should not father a child in this period. For male participants treated with platinum (cisplatin or carboplatin) - pemetrexed, they should not father a child after the last dose of treatment for a period defined as per the local prescribing information. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.

    If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.
20. Participants with known druggable molecular alterations (such as ROS1 translocation or BRAF mutation, KRAS mutation etc.) who might be candidates for alternative targeted therapies as applicable per local regulations and treatment guidelines.
21. Participants with a known documented EGFR genetic aberration (e.g., C797S) mediating resistance to previous treatment with a 3rd generation EGFR TKI (e.g., osimertinib) or any

other known genetic aberration concomitant to MET amplification that could negatively impact the treatment outcome of capmatininb in combination with osimertinib.

22. Participant with known EGFR T790M positive status by either tissue or blood after progression on 1st, 2nd or 3rd generation EGFR TKIs including osimertinib.
23. Participants who received live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, TY21a typhoid vaccines and COVID 19 vaccines) within 30 days prior to the first dose of study treatment.

6 Treatment

6.1 Study treatment

For this study, the investigational drugs are capmatinib and osimertinib. The study treatment refers to the combination of capmatinib and osimertinib, or to platinum (cisplatin or carboplatin) pemetrexed based doublet chemotherapy.

Capmatinib will be labeled and provided to sites by Novartis in compliance with legal requirements for each country.

Osimertinib and platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy will be procured locally according to local practice and regulation.

The study treatment begins on Cycle 1 Day 1 with the first administration of either capmatinib in combination with osimertinib or platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy. For the randomized part (including ET), Cycle 1 Day 1 should occur on the day of the randomization or no later than 3 days after randomization.

All doses prescribed, dispensed to the participant and all dose changes during the study, including the reason, must be recorded on the appropriate electronic case report form (eCRF) page.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Treatment Form or Pharmaceutical Dosage Form	Route of Administration	Presentation	Supply (global or local)
Capmatinib 150 mg or 200 mg	Film-coated tablet	Oral use	Open-label participant specific; bottles	Global
Osimertinib£ 80 mg or 40 mg	Tablet	Oral use	Open-label participant specific; bottles or blister packs	Local
Platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy£	Concentrate for solution for infusion	Intravenous use	Open-label; vials	Local

Investigational/ Control Drug (Name and Strength)	**Treatment Form or Pharmaceutical Dosage Form**	**Route of Administration**	**Presentation**	**Supply (global or local)**
£ provided locally by the study site, subsidiary or designee as commercially available, according to local clinical practices and local regulations. Administration (including related pre-medication schemes for chemotherapy) should follow local prescribing information.				

6.1.2 Additional study treatments

No other treatment beyond investigational drugs (capmatinib and osimertinib) and control drug (platinum -cisplatin or carboplatin- pemetrexed based doublet chemotherapy) are included in this trial.

Platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy (including related pre-medication schemes) should follow local prescribing information.

6.1.3 Treatment arms/group

Run-in part

Up to 2 dose levels of capmatinib in combination with osimertinib may be investigated. The starting dose of combination is capmatinib 400 mg orally twice daily (b.i.d) and osimertinib 80 mg orally once per day (q.d).

If a dose de-escalation is required following DLTs, a lower dose level is defined as capmatinib 400 mg orally twice a day (b.i.d) and osimertinib 40 mg orally once per day (q.d.) (see also Section 6.5).

Capmatinib in combination with osimertinib can be taken with or without food.

A complete cycle of treatment is defined as 21 days of continuous treatment of capmatinib in combination with osimertinib.

Randomized part

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

- Arm 1: capmatinib in combination with osimertinib
  - continuous, oral, daily dosing, with or without food.
  - the starting doses will be the recommended doses for the randomized part (including ET) confirmed during the run-in part.
- Arm 2: platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy, intravenously (i.v.), following local guidelines as per standard of care and products labels (including premedications such as antiemetics, steroids and vitamins)
  - cisplatin 75 mg/m^2 - pemetrexed 500 mg/m^2, or
  - carboplatin AUC5 -AUC 6 - pemetrexed 500 mg/m^2.

Each treatment cycle is 21 days for both arms. First infusion day defines Cycle 1 Day 1. Participants can receive up to 6 cycles of pemetrexed + carboplatin/cisplatin as initial treatment. Participants whose disease has not progressed after four cycles of platinum/pemetrexed based

doublet chemotherapy initial treatment may receive pemetrexed monotherapy maintenance therapy (pemetrexed 500 mg/m^2 on Day 1 of every 21 days cycle) i.v. infusion per product label and local guidelines (as per standard of care).

In Arm 2, participants will be allowed to crossover to receive capmatinib in combination with osimertinib therapy after BIRC-confirmed RECIST 1.1-defined PD, and after meeting the eligibility criteria (see Section 6.1.5.2).

6.1.4 Guidelines for continuation of treatment

Participant should continue to receive the study treatment until one or more criteria for treatment discontinuation described in Section 6.5 and Section 9.1 are met. Guidelines on the management of common capmatinib-osimertinib and platinum pemetrexed based chemotherapy-associated toxicities and dose modification instructions are provided in Section 6.5.

6.1.5 Treatment duration

Participants will be treated until they experience any of the following: unacceptable toxicity, disease progression per RECIST 1.1 (as assessed by the investigator in the run-in part, and as assessed by the investigator confirmed by BIRC in the randomization part), and/or treatment is discontinued at the discretion of the investigator or the participant. A complete list of the circumstances requiring study treatment discontinuation is provided in Section 9.1.1.

Participants who do not tolerate the combination treatment because of unaceptable toxicity that preclude further treatment and are judged by the investigator still to benefit from the treatment could continue to receive either capmatinib or osimertinib as single agent. In such circumstances, participants who permanently discontinued one of the two investigational drugs should still follow the protocol efficacy and safety assessment as scheduled. After discontinuing the two investigational drugs, further treatment is left to the physician's discretion.

Participants may continue the combination treatment of capmatinib + osimertinib beyond locally confirmed disease progression (run-in part) or BIRC-confirmed disease progression (randomized part) if, in the judgment of the investigator, there is evidence of clinical benefit and the participant wishes to continue on the study treatment. Criteria for treatment beyond progression are described in Section 6.1.5.1.

In randomized part, participants in the chemotherapy arm will be allowed to crossover to receive capmatinib in combination to osimertinib therapy after BIRC-confirmed, RECIST 1.1-defined PD. Criteria for crossover to capmatinib in combination to osimertinib therapy are described in Section 6.1.5.2.

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

6.1.5.1 Treatment beyond disease progression

Participants will be permitted to continue the combination treatment of capmatinib + osimertinib beyond disease progression per RECIST 1.1 (as assessed by the investigator in the

run-in part, and as assessed by the investigator confirmed by BIRC in the randomized part), provided they meet all the following criteria:

- Evidence of clinical benefit assessed by investigator
- No rapid radiological or clinical progression
- Tolerance to study treatment
- Should not jeopardize critical interventions to treat/prevent severe complications, or prevent participants from receiving adequate care
- Participant performance status is stable
- Participant written consent to continue on the study treatment
- No new antineoplastic therapy has been initiated

Treatment beyond progression with capmatinib alone or osimertinib alone is not permitted.

The treatment beyond disease progression is only allowed for participants previously treated with the combination of capmatinib + osimertinib.

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

Participants who meet the above criteria and continue the combination of capmatinib + osimertinib treatment beyond initial disease progression per RECIST 1.1 will continue all study procedures as outlined in Section 8. Clinical deterioration or suspicion of further disease progression will require a follow-up imaging assessment to be performed promptly rather than waiting for the next scheduled assessment. Participants who are no longer deriving clinical benefit, or who meet other protocol discontinuation criteria must be discontinued.

Participants who crossed over to capmatinib + osimertinib therapy will also be permitted to continue treatment beyond initial disease progression (radiological progression assessed by the investigator).

6.1.5.2 Crossover to capmatinib in combination with osimertinib therapy

In the randomized part, participants randomized to the platinum-pemetrexed based doublet chemotherapy arm will be allowed to crossover to receive capmatinib in combination with osimertinib therapy after BIRC-confirmed RECIST 1.1-defined PD.

Participants in the platinum-pemetrexed based doublet chemotherapy arm who elect to crossover to capmatinib in combination with osimertinib therapy must follow the study assessments as per visit schedule in Table 8-3 in the ET part.

The following eligibility criteria must be confirmed prior to crossing over to capmatinib in combinatin with osimertinib arm:

- Participants must have recovered from all toxicities related to platinum-pemetrexed based double chemotherapy to grade ≤ 1 (CTCAE version 5.0). Exception to this criterion: participants with any grade of alopecia and vitiligo
- Participants must not have a history or active medical condition of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention)

- Crossover must be performed no later than 84 days of BIRC-confirmed PD. This window is intended to allow the resolution to ≤ CTCAE grade 1 of the toxicity related to the prior chemotherapy with platinum-pemetrexed based doublet chemotherapy
- Participants with CNS metastases must be neurologically stable as specified in exclusion criterion #2 of Section 5.2
- Participants must have an ECOG PS of 0-1
- Participants must not be pregnant
- Participants must be compliant with the contraception guidelines outlined in Section 5.2
- Participants must have adequate organ function including laboratory values (per local laboratory assessment) within 7 days prior to commencing treatment of capmatinib in combination with osimertinib in the ET phase as specified in inclusion criterion #10 of Section 5.1
- Participant must not have clinically significant, uncontrolled heart diseases as specified in exclusion criterion #7 of Section 5.2
- If the participant has not undergone below specified assessment 7 days prior to commencing treatment of capmatinib in combination with osimertinib in the ET phase, they must complete via an unscheduled visit these following assessments in order to ensure the initiation of capmatinib in combination with osimertinib treatment:
  - Vital signs
  - Hematology labs
  - Chemistry labs
  - ECG
  - Cardiac Imaging
  - Adverse events
  - Concomitant medications

Participants must not have started another systemic anti-cancer therapy at the end of the treatment phase. Participants must complete the EOT visit after permanent discontinuation of platinum-pemetrexed based doublet chemotherapy. The ET-EOT visit will be performed for participants who crossover when they permanently discontinue treatment with capmatinib + osimertinib. Participants in ET will be treated until they experience any of the following: unacceptable toxicity, disease progression determined on investigator assessment only, and/or treatment is discontinued at the discretion of the investigator or the participant.

Participants who do not tolerate the combination treatment because of unacceptable toxicity that preclude further treatment and are judged by the investigator still to benefit from the treatment could continue to receive either capmatinib or osimertinib as single agent. In such circumstances, participants who permanently discontinued one of the two investigational drugs should still follow the protocol efficacy and safety assessment as scheduled. After discontinuing the two investigational drugs, further treatment is left to the physician's discretion.

6.2 Other treatment(s)

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

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapy deemed necessary for the care of the participant (i.e., such as anti-emetics, anti-diarrhea) is permitted, except when specifically prohibited (see Section 6.2.2).

The participant must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. All medications (excluding study treatment and prior antineoplastic treatments), blood transfusions, surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose administration of study treatment through 30 days after the last dose of study treatment will be recorded in the Concomitant Medications or Surgical and Medical Procedures eCRF, respectively. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications, food supplements and vitamins. In addition, for participants with CNS lesion who will be evaluated by RANO-BM, corticosteroid use will be documented on the appropriate eCRF (electronic Case Report Form) until disease progression (as determined by investigator and confirmed by BIRC).

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 treatment:

- 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

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

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

- **Strong CYP3A inhibitors:** Coadministrating capmatinib with strong CYP3A inhibitor (itraconazole) increased capmatinib AUC_{inf} by 42%. There was 3% increase in capmatinib C_{max}. Closely monitor participants for adverse reactions during coadministration of capmatinib with strong CYP3A inhibitors.

- **Moderate CYP3A inducers:** Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that coadministration of capmatinib with the moderate CYP3A inducer efavirenz (600 mg once daily for 20 days) would result in a 44% decrease in capmatinib AUC0-12h and 34% decrease in Cmax at steady-state compared to administration of capmatinib alone. Caution should be exercised during concomitant use of capmatinib with moderate CYP3A inducers. Use an alternative medication with no or minimal potential to induce CYP3A during coadministration with capmatinib.
- **CYP1A2 substrates with narrow therapeutic index (NTI):** Capmatinib is a moderate CYP1A2 inhibitor. Coadministration of capmatinib increased sensitive CYP1A2 probe substrate (caffeine) AUC_{inf} by 134%. Avoid coadministration of capmatinib with CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, decrease the CYP1A2 substrate dosage in accordance with the approved prescribing information.
- **P-gp and BCRP substrates:** Coadminstration of capmatinib increased P-gp substrate (digoxin) exposure (AUC_{inf} and C_{max} by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUC_{inf} and C_{max} by 108% and 204%, respectively). Avoid coadministration of capmatinib with P gp and BCRP substrates where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, decrease the P-gp or BCRP substrate dosage in accordance with the approved prescribing information.
- **Proton pump inhibitor:** Coadministration of capmatinib with proton pump inhibitor (rabeprazole) decreased capmatinib AUC_{inf} by 25% and C_{max} by 38%. Exercise caution during concomitant use of capmatinib with proton pump inhibitors.
- **H_2-receptor antagonists and antacids:** As an alternative to proton pump inhibitors, an H_2-receptor antagonist or antacid can be taken. Capmatinib should be administered at least 3 hours before or 6 hours after an H_2- receptor antagonist. Capmatinib should be administered at least 2 hours before or 2 hours after an antacid.

Refer to Section 16.3 Appendix for a list of the medications that require caution when concomitantly used with capmatinib and osimertinib.

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

6.2.1.2 Use of bone modifying agents

Treatment with bone modifying agents (BMAs, e.g., bisphosphonates, denosumab 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 BMAs 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”). Participants taking BMAs prior to entering the study should continue with the same BMA treatment given as per local medical practice.

No drug-drug interaction is expected between study drugs and BMAs, since they are eliminated through different elimination pathways.

6.2.1.3 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.

6.2.2 Prohibited medication

Use of the treatments displayed in this section, Section 16.4 and Section 16.5 are not allowed after the start of the study treatment as stated below.

Drugs with a known risk of Torsades de Pointes (TdP) are prohibited. For identification of drugs with known risk of TdP please refer to qtdrugs.org (refer to Section 16.4).

For participants taking capmatinib and osimertinib, prohibited medications are listed in Section 16.5. Concurrent use of strong CYP3A inducers is prohibited (refer to Section 16.5). Co-administration of capmatinib with strong CYP3A inducer (rifampicin) decreases capmatinib AUC_{inf} by 67% and C_{max} by 56% [CINC280A2102], which may decrease capmatinib anti-tumor activity.

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

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

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

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

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.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for molecular pre-screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a

sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the molecular pre-screening informed consent form, the participant is assigned to the next sequential Participant No. available.

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

The investigator or designated staff will contact the IRT and provide the requested identifying information to register the participant 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 (except if case of re-screening, see Section 8.1). If the subject fails to be enrolled (safety run-in), fails molecular pre-screening, fails to be randomized or to start treatment for any reason, the reason will be entered into the appropriate CRF page.

IRT must be notified within 2 days if the participant did not start treatment or is not randomized.

6.3.2 Treatment assignment, randomization

Run-in part

No randomization will be performed in the run-in part of the trial.

Randomized part

The randomization will be stratified by presence of brain metastasis at baseline (presence vs absence) and prior treatment with 3rd generation EGFR TKIs (yes vs no) and participants will be randomized in a 2:1 ratio to either capmatinib in combination with osimertinib or platinum-pemetrexed based doublet chemotherapy.

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

The study treatment phase begins on Cycle 1 Day 1 with the first administration of capmatinib in combination with osimertinib or platinum-pemetrexed based doublet chemotherapy. Cycle 1 Day 1 should occur on the day of randomization or no later than 3 days after randomization.

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

The threshold for enrollment of different population of participants will be monitored through the IRT system.

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

For participants crossing over from platinum-pemetrexed based doublet chemotherapy to ET in the randomized phase, the study treatment of ET phase begins on Cycle 1 Day 1 with the first administration of capmatinib in combination with osimertinib.

6.4 Treatment blinding

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

6.5 Dose escalation and dose modification

6.5.1 Dose De-escalation guidelines

Information related to Dose Limiting Toxicities (DLTs) is specific to the run-in part of this study.

Information related to dose modification applies to all enrolled participants (run-in and randomized parts).

6.5.1.1 Starting dose

In the safety run in part, the starting dose of the combination is capmatinib (400 mg b.i.d.) and osimertinib (80 mg q.d.). In case that dose de-escalation is required, a lower dose level is defined as capmatinib (400 mg b.i.d.) and osimertinib (40 mg q.d.).

The recommended dose confirmed in the run-in part will be the starting dose for the randomized part and for participants who crossover to ET.

6.5.1.2 Provisional dose levels

Table 6-2 describes the starting dose and the dose levels that may be evaluated during this trial in the run-in part.

Table 6-2 Provisional dose levels

Dose level	Proposed daily dose for osimertinib*	Increment from previous dose
1	80 mg q.d.	(starting dose)
-1*	40 mg q.d.	-50%
*Dose level -1 represents a new treatment dose for osimertinib from the starting dose level. Capmatinib will be administered at 400 mg b.i.d. either at dose level 1 or -1		

6.5.2 Guidelines for confirmation of recommended dose

For the purposes of dose confirmation decisions, each cohort will consist of approximately 10 newly enrolled participants to achieve at least 6 evaluable participants in the dose determining set (DDS, see definition in Section 12.1.5). The first cohort will be treated with the starting dose of capmatinib (400 mg b.i.d.) and osimertinib (80 mg q.d.).

Participants must complete a minimum of 1 cycle (21 days*)* of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the DLT period to be considered evaluable for dose recommendation decisions. Dose recommendation decisions will occur when the cohort of participants has met these criteria.

Dose recommendation 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 ≥ 2 toxicity data during Cycle 1, and PK data from evaluable participants.

Dose confirmation of capmatinib (400 mg b.i.d.) and osimertinib (80 mg q.d.) will occur if the following conditions are met in the safety run-in part:

- At least six evaluable participants treated at this dose and regimen.
- No more than two DLTs have been observed out of six evaluable participants.
- It is the dose recommended for participants after review of all clinical data by Novartis and Investigators in a dose level review team meeting (DLRTM).

If one of the conditions specified above is not satisfied, dose confirmation cannot be declared and a second cohort may be treated at the lower dose level with capmatinib (400 mg b.i.d.) and osimertinib (40 mg q.d.). The same criteria are applied for this new dose and regimen. If dose confirmation cannot be declared on this lower dose, the randomized part cannot start and the study will end.

6.5.2.1 Implementation of dose De-escalation decisions

To implement dose confirmation decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), 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 level review team meeting by teleconference. Drug administration at the next lower dose level or in the randomized part 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 either a lower dose level or to the randomized part.

6.5.2.2 Intra-Participant dose escalation

Intra-participant dose escalation is not permitted at any time.

6.5.3 Definitions of Dose Limiting Toxicities (DLTs) (Run-In Part)

Dose Limiting Toxicities (DLTs) will be collected and used only in the run-in part of the study. A Dose Limiting Toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, progressive disease, inter-current illness, or concomitant medications that despite optimal therapeutic intervention occurs within the first 21 days of treatment with capmatinib in combination with osimertinib and meets any of the criteria included in Table 6-4. Toxicity that is clearly and directly related to the primary disease or another aetiology is excluded by this definition.

National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 5.0 will be used for all grading. For the purpose of dose decisions, DLTs will be considered.

Whenever a particpant experiences a DLT, investigator should follow guidance as per Section 6.5.4 "dose modifications". The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities.

The already characterized toxicity profile of each study drug should be taken into account in the decision process. In Table 6-3 below there is a summary of capmatinib and osimertinib adverse drug reaction by system organ class underlying potential overlapping toxicities (highlighted in bold).

Table 6-3 Capmatinib and osimertinib overlapping toxicities

SOC	**Capmatinib toxicity** (Ref: Core Data Sheet (CDS))	**Osimertinib toxicity** (Ref: United States Prescribing Information USPI)
Blood and lymphatic system disorders		Lymphopenia
		Anemia
		Thrombocytopenia
		Neutropenia
Cardiovascular disorders		QTc Interval Prolongation
		Cardiomyopathy
		Cardiac failure
		Chronic cardiac failure
		Congestive heart failure
		Pulmonary edema
		Decreased ejection fraction
Congenital, familial and genetic disorders	***Embryo-Fetal Toxicity***	***Embryo-Fetal Toxicity***
Eye disorders		Keratitis
Gastrointestinal disorders	***Diarrhoea***	***Diarrhoea***
	Vomiting	***Vomiting***
	Nausea	***Nausea***
	Constipation	***Constipation***
	Amylase increased	Stomatitis
	Lipase increased	
	Acute pancreatitis	
General disorders and *administration site conditions*	***Pyrexia***	***Pyrexia***
	Fatigue	***Fatigue***
	Back pain	***Back pain***
	Oedema peripheral	
	Non-cardiac chest pain	
	Weight decreased	
Hepatobiliary disorders	***ALT increased***	***ALT increased***
	AST increased	***AST increased***
	Blood bilirubin increased	***Hyperbilirubinaemia***
	Hypoalbuminemia	

Infections and infestations	Cellulitis	Upper Respiratory Tract Infection
Metabolism and nutrition disorders	***Decreased appetite***	***Decreased appetite***
	Hyponatremia	***Hyponatremia***
	Hypophosphataemia	Hyperglycemia
		Hypermagnesemia
		Hypokalemia
Nervous system disorders		Headache
Respiratory, thoracic and mediastinal disorders	***Pneumonitis/ILD***	***Pneumonitis/ILD***
	Dyspnoea	***Dyspnoea***
	Cough	***Cough***
Skin and subcutaneous tissue disorders	Urticaria	Rash
	Pruritus	***Pruritus***
		Dry skin
		Nail toxicity
Renal and urinary disorders	Blood creatinine increased	
	Acute kidney injury	

Table 6-4 Criteria for defining dose-limiting toxicities

Criteria for defining dose-limiting toxicities	
Blood and lymphatic system disorders	Febrile neutropenia defined as 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.
	Neutropenia grade 4 regardless of duration
	Thrombocytopenia CTCAE Grade ≥ 3 with bleeding Thrombocytopenia CTCAE Grade 4 regardless of duration or bleeding
	Any other hematologic toxicity = grade 3, present for > 7 consecutive days
	Any other hematologic toxicity ≥ grade 4 present for more than 3 days
Hepatic	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 x ULN] OR [AST or ALT **> 8.0** x ULN], whichever is lower, **combined with** [total bilirubin > 2 x baseline AND > 2.0 x ULN]
Gastrointestinal disorders	Diarrhea ≥ grade 3, nausea or vomiting that DO NOT resolve within 3 days with appropriate maximal medical intervention
Electrolytes	Grade ≥ 3 electrolyte abnormalities that are associated with clinical signs or symptoms and are not reversed with appropriate maximal medical intervention within 3 days
Laboratory abnormalities	≥ grade 3 that result in hospitalization

Skin and subcutaneous tissue disorder	≥ grade 3 despite 7 consecutive days of optimal treatment
Respiratory disorders	≥ grade 2 pneumonitis or interstitial lung disease (ILD) without infection etiology
General disorders	grade 3 fatigue not improving within 7 days
Other adverse events	Any adverse event grade 4 or grade 3 not improving within 7 days. 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. Any death not clearly related to the underlying disease or extraneous causes
* "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold ** "Cholestasis" defined as: ALP (Alkaline Phosphatase) elevation > 2 x ULN 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 5.0 will be used for all grading. Participants may receive supportive care (i.e., transfusion of red blood cells) as per local institutional guidelines, as long as causality can clearly be established that supportive care is to treat disease related events and not related to investigational agent	

6.5.4 Dose modifications

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

The following guidelines should be considered:

Platinum pemetrexed based chemotherapy

Every attempt should be made to maintain the treatment dosing cycle schedule of every 21 days. For participants who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted per the local approved label in order to keep the participant on treatment. Dose reduction will follow the local prescribing information.

Capmatinib and osimertinib

Dose reductions are allowed for capmatinib and osimertinib and should follow the dose reduction steps described in Table 6-5 and Table 6-6. For each participant, a maximum of two consecutive dose level reductions is allowed for capmatinib and one dose level reduction is allowed for osimertinib if starting dose is 80 mg q.d. (no dose level reduction for osimertinib will be allowed if starting dose is 40 mg q.d.) after which the participant must be discontinued.

Dose reductions of capmatinib below 200 mg b.i.d. are not permitted. The lowest dose allowed, 200 mg b.i.d. in tablets is expected to be pharmacologically active, as the observed steady state plasma trough concentrations ([CINC280X1101], [CINC280X2202], n=6) were above the concentration associated with full MET inhibition in xenograft mice models (IC_{90}, 120 nM total concentration). Dose reductions of osimertinib below 40 mg q.d. are not permitted.

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 5.0). Any changes must be recorded on the dosage administration eCRF page.

A participant must discontinue treatment with capmatinib and/or osimertinib if, after treatment is resumed at the lowest allowed dose, the toxicity recurs with the same or worse severity despite use of maximal preventive measures as per the institution guidelines for toxicity prevention and management. Participants who do not tolerate the combination treatment because unacceptable toxicity that preclude further treatment and are judged by the investigator still to benefit from the treatment could continue to receive either capmatinib or osimertinib as single agent. In such circumstances, participants who permanently discontinued one of the two study treatment should still follow the protocol efficacy and safety assessment as scheduled.

Unless otherwise indicated in Table 6-7 and Table 6-8, for grade 1 and tolerable grade 2 treatment-related toxicities, participants may continue full doses of capmatinib and/or osimertinib. For intolerable grade 2 or grade 3 treatment-related toxicities, dosing should be interrupted until at least resolution to grade 1 followed by either dose reduction or re-initiation at the same dose level, as described in Table 6-7. For any grade 4 toxicity except for neutropenia, febrile neutropenia, anemia and thrombocytopenia, participants should interrupt capmatinib and/or osimertinib until resolution to grade 1, followed by either dose reduction or treatment discontinuation (refer toTable 6-7).

If capmatinib and/or osimertinib treatment is withheld because of toxicity for more than 21 consecutive days (counting from the first day when a dose was interrupted), then that treatment should be permanently discontinued (participant may continue on the other treatment alone, provided there is a clinical benefit to participant per investigator judgement). When the investigator believes that continuing treatment may still derive clinical benefit for the participant, study treatment may be resumed. However, the investigator must discuss and receive approval from Novartis Medical Lead or designee prior to continuing study treatment and rationale should be captured in the source documents.

Recommendations for dose reduction or dose interruption of capmatinib/osimertinib in the management of adverse reactions are summarized in Table 6-7 and Table 6-8. Clinical judgement of the treating physician, including confirmation of laboratory values if deemed necessary, should guide the management plan of each participant based on individual risk/benefit assessment. However, permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-7 and Table 6-8, or listed in Section 6.5.2. Deviations to mandatory dose discontinuations are not allowed.

If capmatinib is permanently discontinued and participant continues osimertinib as monotherapy, please refer to the current local prescribing information for dose modifications.

For confirmed pneumonitis and interstitial lung disease, both capmatinib and osimertinib must be permanently discontinued.

Careful assessment of all participants with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD/pneumonitis. Study treatment should be interrupted pending investigation of these symptoms. If ILD/pneumonitis is diagnosed, study treatment should be permanently discontinued and appropriate treatment initiated as necessary. Reintroduction of study treatment should be considered only in the absence of a diagnosis of ILD/pneumonitis and after careful consideration of the individual participant's benefits and risks.

Dose re/escalation of study treatment to previous dose is not allowed.

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

	Starting Dose level 0	**Dose level -1**	**Dose level -2**
capmatinib	400 mg b.i.d.	300 mg b.i.d.	200 mg b.i.d.

Table 6-6 Dose reduction steps for osimertinib

	Starting dose level 0	**Dose level -1**
Osimertinib	80 mg q.d.	40 mg q.d.
Note: dose reduction should be based on the worst toxicity demonstrated at the last dose.		

If osimertinib starting dose for randomized part is 40 mg q.d. (dose level 0), no dose reduction (dose level -1) is permitted.

Table 6-7 Dose modifications for capmatinib in combination with osimertinib

Worst toxicity CTCAE[a] Grade (**value**)	**Recommendation**
Investigations (**Hematologic**)	
Neutropenia (**ANC**)	
Grade 1 (ANC < lower limit of normal (LLN) - 1500/mm^3; < LLN - 1.5 x 10^9/L)	Maintain dose levels of both study drugs.
Grade 2 (ANC < 1500 - 1000/mm^3; < 1.5 - 1.0 x 10^9/L)	Maintain dose levels of both study drugs.
Grade 3 (ANC < 1000 – 500/mm^3)	Omit study treatment until resolved to ≤ grade 2, then resume osimertinib at the same dose level. • If fully resolved in ≤ 7 days, then resume capmatinib at the 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 osimertinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 2, then resume osimertinib 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 toxicity during osimertinib monotherapy, omit study treatment until resolved to ≤ grade 2, then resume osimertinib at ↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of osimertinib monotherapy at ↓ 1 dose level, resume capmatinib at same dose level
Grade 4 (ANC < 500/mm^3)	Omit study treatment until resolved, then resume osimertinib at the same dose level. • If no recurrence of grade 3 toxicity or higher after 7 days of osimertinib monotherapy, resume capmatinib at ↓ 1 dose level

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	• If recurrence of grade 3 or higher toxicity on maintained dose level of osimertinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 2, then resume osimertinib at ↓ 1 dose level and capmatinib at the same dose level (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 osimertinib monotherapy, omit study treatment until resolved to ≤ grade 2, then resume osimertinib at ↓ 1 dose level • If no recurrence of grade 3 or higher toxicity after 7 days of osimertinib monotherapy at ↓ 1 dose level, resume capmatinib at the same dose level
Febrile Neutropenia	
ANC < 1000/mm^3 and a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour	Omit study treatment until resolved, then resume osimertinib 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 osimertinib monotherapy, omit osimertinib until resolved, then resume osimertinib ↓ 1 dose leveland capmatinib at ↓ 1 dose level
Platelet (PLT) count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75,000/mm^3; < LLN - 75 x 10^9/L)	Maintain dose levels of both study drugs.
Grade 2 (PLT < 75,000 - 50,000/mm^3; < 75 - 50 x 10^9/L)	Maintain dose levels of both study drugs.
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Omit study treatment until resolved to ≤ grade 2, then resume osimertinib 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 during osimertinib monotherapy, omit study treatment until resolved to ≤ grade 2, then resume osimertinib at ↓ 1 dose level and capmatinib at same dose level
Grade 4 (PLT < 25,000/mm^3)	Omit study treatment until resolved to ≤ grade 2, then resume osimertinib at the same dose level. • If no recurrence of grade 3 or higher toxicity after 7 days of osimertinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 or higher toxicity on maintained dose level of osimertinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 2, then resume osimertinib 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 4 AE)

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

Worst toxicity CTCAE[a] Grade (**value**)	**Recommendation**
Grade 4 (> 6.0 × ULN)	Discontinue capmatinib permanently and omit osimertinib until resolved to ≤ grade 1 or baseline, then resume osimertinib at the same dose level
Investigations (**Hepatic**)	
Isolated Total Bilirubin[b]	
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose levels of both study drugs
Grade 2 (> 1.5 and ≤ 3.0 × ULN) with ALT or AST ≤ 3.0 × ULN, in participants with normal isolated total bilirubin value at baseline	Omit study treatment until resolved to ≤ grade 1, then resume both study drugs at the same dose level
Grade 3 (> 3.0 and ≤ 10.0 × ULN)	Omit study treatment until resolved to ≤ grade 1, then resume osimertinib at the same dose level. • If no recurrence of grade 3 toxicity after 7 days of osimertinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 toxicity on maintained dose of osimertinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 1, then resume osimertnib 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 3 AE) • If recurrence of grade 3 toxicity during osimertinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume osimertinib at ↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of osimertinib monotherapy at ↓ 1 dose level, resume capmatinib at ↓ 1 dose level
Grade 4 (> 10.0 × ULN)	Discontinue capmatinib permanently and omit osimertinib until resolved to ≤ grade 1, then resume osimertinib at the same dose level. Monitor for recurrence 7 days after resumption of osimertinib, or sooner if clinically indicated. • If Grade 3 or higher elevation recurs, omit osimertinib until resolved to ≤ grade 1, then resume osimertinib at ↓ 1 dose level. • If Grade 4 or higher elevation recurs, discontinue osimertinib permanently.
Isolated AST or ALT	
Grade 2 (> 3.0 and ≤ 5.0 × ULN) without total bilirubin elevation to > 2.0 × ULN, for participants with normal AST/ALT values at baseline	Maintain dose level of both drugs with Liver function test LFTs[c] monitored per protocol
Grade ≥3 (> 5.0 × ULN) without total bilirubin elevation to > 2.0 × ULN	Omit study treatment until resolved to ≤ grade 1, then resume osimertinib at the same dose level. • If no recurrence of grade 3 toxicity after 7 days of osimertinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of grade 3 toxicity on maintained dose of osimertinib and at ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 1, then resume osimertinib 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 3 AE)

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	• If recurrence of grade 3 toxicity during osimertinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume osimertinib at ↓ 1 dose level • If no recurrence of grade 3 toxicity after 7 days of osimertinib monotherapy at ↓ 1 dose level, resume capmatinib at ↓ 1 dose level
Combined[d,e] elevation of AST or ALT and concurrent Total bilirubin[f]	
For participants with normal baseline ALT or AST or 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 osimertinib 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[c], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilized over 4 weeks. Following resolution of AST, ALT, and bilirubin to ≤ grade 1 (or to baseline), osimertinib may be resumed at ↓ 1 dose level if considered by the investigator to be in the best interest of the patient and following documented discussion with Novartis. Monitor LFTs twice weekly for two weeks and then weekly for two weeks after resumption.
Investigation (metabolic)[g]	
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 osimertinib 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 osimertinib monotherapy, omit study treatment until resolved to ≤ grade 2, then resume osimertinib at ↓ 1 dose level • If no recurrence of Grade 3 toxicity after 7 days of osimertinib 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 osimertinib until resolved to grade ≤ 2, then resume osimertinib at the same dose level. 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.	
Cardiac Investigations	
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 the same dose level and osimertinib at ↓ 1 dose level

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	• If resolved in > 7 days, resume both study drugs at ↓ 1 dose level
Grade 4 ([QT/QTc ≥ 501 or > 60 ms change from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia])	Permanently discontinue capmatinib and osimertinib. Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to < 481 ms.
Left ventricular ejection fraction decrease	
Asymptomatic, absolute decrease in LVEF of > 10% that is also below institutional lower limits of normal (LLN)	Omit osimertinib, maintain capmatinib dose level, obtain consultation with Cardiologist, and repeat cardiac imaging after 1-2 weeks • If improved to 10% or less from baseline and at least at institutional LLN within 4 weeks, then resume osimertinib at ↓ 1 dose level. • Repeat ECHO or MUGA 2, 4, 8, and 12 weeks after re-starting osimertinib. If no recurrence of LVEF decline and if agreed by Cardiologist, the frequency of LVEF monitoring may then be decreased to the standard schedule per Table 8-2 and Table 8-3. If not improved to 10% or less from baseline and at least at institutional LLN within 4 weeks, then discontinue osimertinib
Grade 3 left ventricular systolic dysfunction	Omit study treatment and obtain consultation with Cardiologist. Following resolution of symptoms and recovery of the LVEF to the normal range, capmatinib may be resumed at the same dose level with repeat cardiac imaging 2 weeks after resumption, if agreed by Cardiologist. If recovery of LVEF occurred within 4 weeks and remains normal after 2 weeks of capmatinib treatment, osimertinib may be resumed at ↓ 1 dose level, if agreed by Cardiologist. Repeat ECHO or MUGA 2, 4, 8, and 12 weeks after resumption of capmatinib. If no recurrence of LVEF decline and if agreed by Cardiologist, the frequency of LVEF monitoring may then be decreased to the standard schedule per Table 8-2 and Table 8-3.
Grade 4 left ventricular dysfunction	Discontinue study treatment and obtain consulation with Cardiologist.
NOTE: Upon discontinuation due to LVEF decrease, closely monitor LVEF until resolution. The same cardiac imaging modality (i.e., transthoracic echocardiography (TTE) or multigated acquisition (MUGA) scan) used at baseline is to be used for all subsequent assessments.	
Cardiac Biomarkers	
NT-Pro-BNP elevation, any grade	Maintain the dose of capmatinib. Omit osimertinib and evaluate and treat patient per institutional guidelines. Evaluate LVEF with TTE or MUGA. Follow NT-Pro-BNP to resolution per institutional guidelines, or at least weekly. If no evidence of LVEF decrease from baseline of 10% or greater to below institutional LLN on TTE or MUGA, then resume dose levels of capmatinib and osimertinib. Consult with Cardiologist. If evidence of LVEF decrease from baseline of 10% or greater to below institutional LLN on TTE or MUGA, follow guidelines for LVEF decrease.

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
Troponin I/T elevation, any grade	Maintain the dose of capmatinib. Omit osimertinib and evaluate and treat patient per institutional guidelines. Evaluate LVEF with TTE or MUGA. Follow Troponin I/T to resolution per institutional guidelines. If no evidence of LVEF decrease from baseline of 10% or greater to below institutional LLN on TTE or MUGA, then resume dose level. Consult with Cardiologist. If evidence of LVEF decrease from baseline of 10% or greater to below institutional LLN on TTE or MUGA, follow guidelines for LVEF decrease.
Vascular disorders	
Hypertension CTCAE grade 3 for at least 7 days, despite treatment	Omit osimertinib until resolved ≤ grade 1, and 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 osimertinib at ↓ 1 dose level after 7 days of capmatinib monotherapy, resume osimertinib 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 osimertinib at ↓ 1 dose level
CTCAE grade 4	Discontinue patient from capmatinib and osimertinib
Gastro intestinal	
Diarrhea[h]	
Grade 1	Maintain dose levels of both study drugs but institute anti-diarrheal treatment
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose of both study drugs 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 the same dose level • If no recurrence of Grade 3 toxicity after 7 days of capmatinib monotherapy, resume osimertinib at ↓ 1 dose level • If recurrence of Grade 3 toxicity during capmatinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume capmatinib at ↓ 1 dose level • If no recurrence of Grade 3 toxicity after 7 days of capmatinib monotherapy at ↓ 1 dose level, resume osimertinib 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 osimertinib at the same dose level • If no recurrence of Grade 3 or higher toxicity after 7 days of osimertinib monotherapy, resume capmatinibat at ↓ 1 dose level

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	• If recurrence of Grade 3 or higher toxicity during osimertinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume capmatinib at ↓ 1 dose level • If no recurrence of Grade 3 or higher toxicity after 7 days of capmatinib monotherapy at ↓ 1 dose level, resume osimertinib at the 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 osimertinib at the same dose level • If no recurrence of Grade 3 toxicity after 7 days of osimertinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of Grade 3 toxicity during osimertinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume capmatinib at ↓ 1 dose level • If no recurrence of Grade 3 toxicity after 7 days of capmatinib monotherapy at ↓ 1 dose level, resume osimertinib 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 toxicities	
Stevens-Johnson Syndrome (SJS) or Lyell syndrome/Toxic Epidermal Necrolysis (TEN)	Permanently discontinue study treatment and manage per institutional guidelines.
Rash	
Grade 1 Macules/papules covering < 10% BSA (Body Surface Area)	Maintain dose levels of both study drugs
Grade 2 Macules/papules covering 10 - 30% BSA	Maintain dose levels of both study drugs
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 osimertinib at ↓ 1 dose level • If recurrence of Grade 3 toxicity during capmatinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume capmatinib at ↓ 1 dose level • If no recurrence of Grade 3 toxicity after 7 days of capmatinib monotherapy at ↓ 1 dose level, resume osimertinib at same dose level
Pneumonitis/Interstitial lung disease	
Grade 1	Omit 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 study treatment.

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	Only in the absence of a diagnosis of ILD/Pneumonitis, study treatment may be resumed at the same dose level. If recurrence after resumption of study drugs, permanently discontinue study treatment.
Grade 2	Mandatory: omit study treatment 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 study treatment. Only in the absence of a diagnosis of ILD/Pneumonitis, study treatment may be resumed following these guidelines: • If resolves to ≤ Grade 1 in ≤ 7 days, resume study drugs both at ↓ 1 dose level • If fails to resolve to ≤ Grade 1 within 7 days or recur after resumption of study drugs at ↓ 1 dose level, permanently discontinue study treatment.
Grade 3 OR Grade 4	Permanently discontinue study treatment.
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	Maintain dose levels of both study drugs
Grade 3	Omit study treatment until resolved to ≤ grade 1, then resume osimertinib at the same dose level. • If resolved in ≤ 7 days, then resume capmatinib at the same dose level • If resolved in > 7 days, then resume capmatinib at ↓ 1 dose level • If recurrence of Grade 3 toxicity during osimertinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume osimertinib at ↓ 1 dose level • If no recurrence of Grade 3 toxicity after 7 days of osimertinib monotherapy at ↓ 1 dose level, resume capmatinib at the same dose level
Peripheral edema	
Grade 1 or 2	Maintain dose levels of both study drugs
Grade 3	Omit study treatment until resolved to ≤ grade 1, then resume osimertinib at the 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 osimertinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of Grade 3 toxicity on maintained dose of osimertinib 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 osimertinb (i.e., 2 ↓ dose level of capmatinib and maintained dose level of osimertinib from the initial occurrence of grade 3 toxicity) • If recurrence of Grade 3 toxicity during osimertinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume osimertinib at ↓ 1 dose level

Worst toxicity CTCAE[a] Grade (**value**)	**Recommendation**
	• If no recurrence of Grade 3 toxicity after 7 days of osimertinib monotherapy at ↓ 1 dose level, resume capmatinib at ↓ 1 dose level
Grade 4	Permanently discontinue capmatinib and continue osimertinib monotherapy
Metabolic	
Any Grade **hypophosphatemia**	Treatment with phosphate supplements as clinically indicated and maintain dose levels of both study drugs
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 the same dose level and osimertinib at ↓ 1 dose level • If resolved in > 14 days, then permanently discontinue patient from osimertinib and resume capmatinib at the same dose level.
Grade 4 Uveitis/Retinopathy	Permanently discontinue osimertinib and refer the patient to an ophthalmologist for monitoring. Resumption of osimertinib 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 osimertinib and refer the patient to an ophthalmologist immediately for monitoring. Resumption of osimertinib following resolution to ≤ grade 1 may be considered if approved by ophthalmologist and after documented discussion with Novartis. Resume capmatinib at the same dose level upon resolution to ≤ grade 1.
Other ocular/visual toxicity	
Grade 1 or 2	Maintain dose levels of both study 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 the same dose level and osimertinib at ↓ 1 dose level • If resolved in > 14 days, then discontinue patient from osimertinib and resume capmatinib at ↓ 1 dose level.
Grade 4	Permanently discontinue osimertinib, omit capmatinib and refer the patient to an ophthalmologist immediately for monitoring. Resumption of osimertinib at ↓ 1 dose level following resolution to ≤ grade 1 may be considered if approved by ophthalmologist and after documented discussion with Novartis.

Worst toxicity CTCAE[a] Grade (value)	**Recommendation**
	Once resolved to ≤ grade 1, resume capmatinib.
Other adverse events	
Grade 1 or 2	Maintain dose levels of both study drugs
Grade ≥ 3	Omit study treatment until resolved to ≤ grade 1, then resume osimertinib at the same dose level and re-evaluate after 7 days, or sooner if clinically indicated • If no recurrence of Grade 3 or higher toxicity after 7 days of osimertinib monotherapy, resume capmatinib at ↓ 1 dose level • If recurrence of Grade 3 or higher toxicity on maintained dose level of osimertinib and ↓ 1 dose level of capmatinib, omit study treatment until resolved to ≤ grade 1, then resume osimertinib 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 3 AE) • If recurrence of Grade 3 or higher toxicity during osimertinib monotherapy, omit study treatment until resolved to ≤ grade 1, then resume osimertinib at ↓ 1 dose level • If no recurrence of Grade 3 or higher toxicity after 7 days of osimertinib 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. [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 transferase (GGT). For isolated elevations of any grade of alkaline phosphatase and/or GGT, maintain dose level. [d] "Combined" defined as: total bilirubin increase 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. [g] A CT (Computerized Tomography) 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. [h] Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.

Table 6-8 Dose modifications for capmatinib (if osimertinib 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 the same dose level If fully 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/mm^3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour	Omit dose, then: If resolved in ≤ 7 days, resume treatment at ↓ 1 dose level If resolved in > 7 days, permanently discontinue participant from capmatinib treatment
Hemoglobin decreased (Anemia)	
Grade 1 (Hemoglobin [Hgb] < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L)	Maintain dose level
Grade 2 (Hgb < 10.0 - 8.0 g/dL; < 6.2 – 4.9 mmol/L; < 100 - 80 g/L)	Maintain dose level
Grade 3 (Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated)	Omit dose until resolved to ≤ grade 2, then: If 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 (Life-threatening consequences; urgent intervention indicated)	Omit dose until resolved to ≤ grade 2 and then resume at ↓ 1 dose level If grade 3 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 treatment at the same dose level.
Grade 3 (> 3.0 - 6.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume 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 the 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: [AST or ALT > 3 x baseline] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN] without evidence of cholestasis or hemolysis	Mandatory: Permanently discontinue capmatinib treatment
METABOLIC	
Amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN; > 2.0 - 5.0 x ULN and asymptomatic)	Maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms; > 5.0 x ULN and asymptomatic)	Omit the dose until resolved to ≤ grade 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 fully 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 the 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 the 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
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 resolved in ≤ 7 days, then resume at ↓ 1 dose level If 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 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 resumed following 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
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue/ Asthenia	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, resume at the same dose level If resolved in > 7 days, resume at ↓ 1 dose level
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 ADL), consider omitting the dose until resolved to ≤ grade 1, then resume either at the 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)	

6.5.4.1 Dose adjustments for QTcF prolongation

Please see Table 6-7 and Table 6-8.

6.5.5 Follow-up for toxicities

All participants will be followed for safety until 30 days after the last dose of study treatment. Participants whose treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event. Appropriate clinical experts such as ophthalmologists, endocrinologists, dermatologists, psychiatrists etc., should be consulted as deemed necessary.

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 6-9 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 has resolved to baseline or stabilization over 4 weeks
Isolated AST/ALT elevation	AST/ALT CTCAE Grade 2 elevation: For participants with baseline value ≤ 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 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.

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

TOXICITY	FOLLOW-UP EVALUATION
	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 (i.e., discontinuation of concomitant medication, dietary modification, treatment of comorbidity). The participant should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practice and the investigator's best judgment and may follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004). For example: For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at a standard dose (e.g., initial administration of 4 mg, then 2 mg every 2-4 hr, maximum of 16 mg/day), along with oral hydration and dietetic measures should be considered. Note: complicating signs or symptoms include moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration. For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms), management should involve intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg sub-cutaneous tid or 25 to 50 µg/h IV) and antibiotics (i.e., fluoroquinolone) should be given

TOXICITY	**FOLLOW-UP EVALUATION**
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 (i.e., 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 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

TOXICITY	FOLLOW-UP EVALUATION
	Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated) [b]
CTCAE Grade 3 and Grade 4	CT scan (high-resolution with lung windows) Clinical evaluation and laboratory work-up for infection Consult pulmonologist Pulmonary function tests[a] - if < normal, repeat every 8 weeks until ≥ normal Bronchoscopy with biopsy and/or BAL if possible[c] Treat with IV steroids (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, a high dose 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] PFT (Pulmonary function tests) to include: diffusing capacity for carbon monoxide corrected for hemoglobin (DLCO); spirometry; resting oxygen saturation. Guideline for significant deterioration in lung function: Decrease in spirometry and/or DLCO of 30% and/or O_2 saturation ≤ 88% at rest on room air. [b] Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. Consider tapering dosage at end. [c] If bronchoscopy is performed, bronchoalveolar lavage (BAL) should be done where possible to exclude alveolar hemorrhage, opportunistic infections, cell count + determination lymphocyte CD4/8 count where possible.	

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

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

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

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

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

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

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, Glutamate dehydrogenase (GLDH), prothrombin time (PT)/ International Normalized Ratio (INR), alkaline phosphatase, albumin, and creatine kinase.

Evaluate status of liver metastasis (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 metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 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 6-10 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-10 Guidance to rule out other alternative causes of observed LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	• Immunoglobulin IgM anti-HAV; Hepatitis B surface antigen (HBsAg), IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV (Hepatitis E Virus), 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, 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

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, Thyroid Stimulating Hormone (TSH); CVD (Cardio Vascular Diseases) / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes (T1D) / glycogenic hepatitis.

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

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Every time the study treatment is to be administered, IRT needs to be accessed (please refer to the IRT manual). The date and time of study treatment administration during the study and any deviations from the protocol treatment schedule will be captured on the appropriate study treatment dispensing form. The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

For treatment with platinum - pemetrexed based doublet chemotherapy: exposure to the study treatment will be based on the number of infusions administered.

For treatment with capmatinib in combination with osimertinib: compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in a drug accountability log.

In the case where study treatment is administered at a remote location by an off-site healthcare provider, treatment administration compliance will be assessed by the off-site healthcare professional and information provided to the Investigator and/or study personnel.

6.6.2 Emergency breaking of assigned treatment code

Not applicable

6.7 Preparation and dispensation

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

Capmatinib

The investigator or responsible site personnel must instruct the participant or caregiver to take the study treatment as per protocol. Study treatment will be dispensed to the participant by

authorized site personnel only. All dosages prescribed to the participant and all dose changes during the study must be recorded on the study treatment eCRF.

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

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

Osimertinib

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

Platinum pemetrexed based doublet chemotherapy

Preparation and dispensation of cisplatin, carboplatin or penetrexed should follow local guidelines as per standard of care and product labels.

As per Section 4.6 during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP (capmatinib and osimertinib) directly to a participant's home is generally permitted (if allowed by Local or Regional Health Authorities and Ethics Committees) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. Platinum pemetrexed should be shipped and administered in an authorized hospital environment or in a similar structure. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. The shipment/provisioning will be for a maximum of 3 months supply. In this case, regular phone calls or virtual contacts (every 3 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, drug accountability, safety monitoring including safety assessments, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant´s health status until the participant can resume visits at the study site.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

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

The investigator or designated site staff must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. The Investigator must provide accountability also for locally sourced materials used for administration. If study treatment is administered at home e.g., capmatinib and osimertinib, participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the site may destroy and document destruction of unused study treatment, drug labels and packagings as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable

6.7.2 Instruction for prescribing and taking study treatment

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

Table 6-11 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	**Dose**	**Frequency and/or Regimen**
Capmatinib (INC280) 200 mg or 150 mg	400 mg orally (2 x 200 mg or 2 x 150 mg [if dose is reduced to 300 mg b.i.d.], if applicable)	Twice daily
Osimertinib 80 mg or 40 mg	80 mg or 40 mg orally	Once daily
Cisplatin/carboplatin pemetrexed based doublet chemotherapycombination (as per local product available)	pemetrexed 500mg/m^2 + carboplatin AUC 5-AUC 6 or pemetrexed 500mg/m^2 + cisplatin 75mg/m^2 administered intravenously (i.v.) following local guidelines as per standard of care and product labels. Participants can receive up to 6 cycles of pemetrexed + carboplatin/cisplatin as initial treatment. Participants whose disease has not progressed after four cycles of platinum-based first-line chemotherapy initial treatment may receive pemetrexed maintenance therapy (pemetrexed 500mg/m^2 on Day 1 of every 21 days cycle). i.v. infusion per product label and local guidelines (as per standard of care)	Once every 21 days

6.7.2.1 Dose and Treatment Schedule

6.7.2.1.1 Capmatinib - Osimertinib

The investigator must instruct the participant to take the study drugs exactly as prescribed. All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the dosage administration eCRF. A complete cycle of treatment is defined as 21 days of twice daily treatment with capmatinib and 21 days of once daily treatment with osimertinib.

Capmatinib tablets will be administered orally on a continuous twice daily (b.i.d.) dosing schedule, on a flat scale of mg per administration and not individually adjusted by weight or body surface area. Osimertinib tablets will be administered orally on a continuous once daily dosing schedule, also on a flat scale and at the same time as the morning dose of capmatinib. Refer to Table 6-11.

Each dose of capmatinib or capmatinib plus osimertinib is to be taken with a glass of water (at least 8 ounces – approximately 240 mL) and consumed over as short a time as possible (i.e., not slower than 1 tablet every 2 minutes).

Capmatinib and capmatinib plus osimertinib 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 days of PK sampling, doses of capmatinib plus osimertinib must be held and taken in the clinic, as instructed by study personnel. On these days, capmatinib plus osimertinib will be administered at the site in the morning prior to the post-dose PK sample blood draws supervised by a member of the research team. The pre-dose PK samples will be taken right before capmatinib plus osimertinib administration. The exact time of drug administration must be recorded in the appropriate eCRF. Information of whether capmatinib was administered with or without food must be recorded in the appropriate eCRF. If a participant vomits within 4 hours of capmatinib dosing on the day of post-dose PK blood sampling, PK sample collection is at investigator's discretion. If PK sample collection is performed, the time of vomiting should be recorded on the eCRF (this does not apply for participants in ET, since no PK sample is collected).

Participants must be instructed not to make up for missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 4 hours of the scheduled capmatinib twice daily dosing. If that occurs, then the dose (or part remaining dose) should not be taken and dosing should restart with the next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose.

Osimertinib will be supplied locally as commercially available and labeled accordingly to comply with legal requirements of each country. Osimertinib administration should follow local prescribing information if not differently reported in this protocol. Refer to Table 6-11.

During the whole duration of treatment with capmatinib plus osimertinib, the participant is recommended to use precautionary measures against ultraviolet exposure (i.e., use of sunscreen, protective clothing, avoid sunbathing or using a solarium).

6.7.2.1.2 Platinum premetrexed based doublet chemotherapy

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

6.7.2.2 Osimertinib

Osimertinib will be supplied locally as commercially available and labeled accordingly to comply with legal requirements of each country. Osimertinib administration should follow local prescribing information if not differently reported in this protocol.

7 Informed consent procedures

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

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

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). A copy of the ICFs must be provided to the participant (or the legally authorized representative). The process of obtaining informed consent must be documented in the participant source documents.

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

Participants who are re-screened are required to sign a new ICF.

Information about common side effects already known about the investigational treatment can be found in the [capmatinib Investigator's Brochure] or in the Core Data Sheet (CDS)/package insert for licenced or approved drug.

This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also during the study as needed. The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant (or the legally authorized representative) and answer all questions regarding the study.

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

The following informed consents are included in this study:

- Molecular pre-screening consent
- Main study consent, which also includes a subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- Treatment beyond progression (only applicable for capmatinib + osimertinib arm, including ET)
- As applicable, Home Nursing consent

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

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information. This will be applicable for both arms (capmatinib + osimertinib and platinum - pemetrexed arms).

A copy of the approved version of all consent forms must be provided to Novartis after Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) approval.

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

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

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

In case the situation limits or prevents on-site study visits and if home nursing (as outlined in Section 8) is implemented, depending on local regulations and capabilities, a separate Home nursing consent must be used in addition to the main Global ICF.

8 Visit schedule and assessments

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

Written informed consent must be obtained before any study specific assessments are performed, including those at molecular pre-screening and screening. Main screening evaluations and baseline radiological tumor assessments should be performed within 28 days of treatment start. All visits are to be scheduled according to the appropriate number of calendar days from Cycle 1 Day 1 of study treatment administration.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-2 and Table 8-3) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who discontinue from study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

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

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g., teleconsult) or visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

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

Table 8-1 Visit Window

Visit Name	Window allowed
Screening	-28 days to -1 day from first dose of study treatment
Cycle 1 Day 1	Within 3 days after randomization (for randomized part)
Day 1 of all subsequent cycles and ET cycles	±3 days
Imaging evaluations	±7 days
PRO assessments	• During the treatment and until progression: within 3 days prior to the visit

Visit Name	**Window allowed**
	• For EOT and post progression time points: ±7 days of the visit
EOT and ET EOT	≤ 7 days after stopping study treatment for EOT
30-Day Safety Follow-Up Period (FUP)	+7 days
Survival FUP	± 14 days
Laboratory assessments performed as part of the screening evaluations will not be required to be repeated on the first day of dosing (Cycle 1 Day 1) (except hematology/chemistry, serum pregnancy test, ECG* and ECHO/MUGA, if not done within 15 days prior to treatment start) unless deemed clinically necessary by the investigator and/or required as per local institutional policies. * ECG for run-in part will be required to be repeated at screening and at C1D1 due to multiple ECGs required at C1D1. Every effort must be made to follow the schedule of assessments (Table 8-2 and Table 8-3) within the windows outlined in Table 8-1 or as close to the designated day/time as possible. If a given visit is out of window, the next visit should be performed with reference to the day of first dose in order to get the participant back on schedule. If an off-schedule imaging assessment is performed, subsequent imaging assessments should be performed in accordance with the original imaging schedule.	

Table 8-2 Assessment Schedule, Part 1

Period	**Screening**		**Treatment: Capmatinib and osimertinib**				**EOT**	**Follow-up**		
Cycle			**Cycle 1 (Cycle 1)**			**Cycle 2 (Cycle 2 and beyond)**				
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 2**	**Cycle 1 Day 15**	**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Tumor and PROs FUP**	**End of post treatment FUP**
Visit Numbers[1]	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**
Days	**-**	**-28 to -1**	**Day 1**	**2**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
Informed consent for molecular pre-screening	X									
Informed consent for treatment beyond progression			X (participants who meet the criteria outlined in Section 6.1.5.1)							
[redacted]										

Period	**Screening**		**Treatment: Capmatinib and osimertinib**				**EOT**	**Follow-up**		
Cycle			**Cycle 1 (Cycle 1)**			**Cycle 2 (Cycle 2 and beyond)**				
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 2**	**Cycle 1 Day 15**	**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Tumor and PROs FUP**	**End of post treatment FUP**
Visit Numbers[1]	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**
Days	**-**	**-28 to -1**	**Day 1**	**2**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
[redacted]										
IRT pre-screening registration	X									
Inclusion / Exclusion criteria	X	X								
IRT eligibility check		S								
IRT registration		X	X			X	X			
Main informed consent		X								
Demography	X									
Medical history/current medical conditions		X								
Diagnosis and stage of cancer	X									
Smoking history		X								
Prior antineoplastic therapy (meds, surgery, radiation)		X								

Period	**Screening**		**Treatment: Capmatinib and osimertinib**				**EOT**	**Follow-up**		
Cycle			**Cycle 1 (Cycle 1)**			**Cycle 2 (Cycle 2 and beyond)**				
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 2**	**Cycle 1 Day 15**	**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Tumor and PROs FUP**	**End of post treatment FUP**
Visit Numbers[1]	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**
Days	**-**	**-28 to -1**	**Day 1**	**2**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
Prior/concomitant medications		Continuously from 28 days prior to first dose until 30 days after last dose of study treatment								
Physical examination, including neurological exams		S	As clinically indicated							
Targeted physical examination			S		S	S	S			
ECOG performance status		X	X			X	X			
Body Height		X								
Body Weight		X	X		X	X	X			
Vital Signs		X	X		X	X	X			
HIV history (HIV testing where locally required)		S								
Hematology[3]		X (≤ 72 hr before C1D1)	X		X	X	X			
Clinical chemistry[3]		X (≤ 72 hr before C1D1)	X		X	X	X			
Coagulation panel[3]		X (≤ 72 hr before C1D1)	As clinically indicated							
Urinalysis (dipstick)[3]		X	As clinically indicated							
Pregnancy Test (serum)		S (≤ 72 hr before C1D1)					S			

Period	**Screening**		**Treatment: Capmatinib and osimertinib**				**EOT**	**Follow-up**		
Cycle			**Cycle 1 (Cycle 1)**			**Cycle 2 (Cycle 2 and beyond)**				
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 2**	**Cycle 1 Day 15**	**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Tumor and PROs FUP**	**End of post treatment FUP**
Visit Numbers[1]	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**
Days	**-**	**-28 to -1**	**Day 1**	**2**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
Pregnancy test (urine)						S				
CT or MRI Chest and Abdomen		X				X Starting at cycle 3 day 1 and then every 6 weeks (+/- 7 days) for the first 18 months after C1D1, then every 12 weeks (+/- 7 days) until PD determined using RECIST 1.1 by local investigator	X EOT scan not required if previous scan was performed ≤ 28 days		X	
Brain CT or MRI		X				X If brain lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.	X EOT scan not required if previous scan was performed ≤ 28 days		X If brain lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.	

Period	**Screening**		**Treatment: Capmatinib and osimertinib**				**EOT**	**Follow-up**		
Cycle			**Cycle 1 (Cycle 1)**			**Cycle 2 (Cycle 2 and beyond)**				
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 2**	**Cycle 1 Day 15**	**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Tumor and PROs FUP**	**End of post treatment FUP**
Visit Numbers[1]	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**
Days	**-**	**-28 to -1**	**Day 1**	**2**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
CT or MRI of other metastatic sites (e.g., neck)		X (mandated for any metastatic sites not captured by CT/MRI of chest, abdomen, and brain)				X If lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.	X EOT scan not required if previous scan was performed ≤ 28 days		X If lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated	
CT or MRI Pelvis		X				X If pelvic lesion present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.	X EOT scan not required if previous scan was performed ≤ 28 days		X If pelvic lesion present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.	
Whole Body Bone scan		X	If clinically indicated						If clinically indicated	

Period	**Screening**		**Treatment: Capmatinib and osimertinib**				**EOT**	**Follow-up**		
Cycle			**Cycle 1 (Cycle 1)**			**Cycle 2 (Cycle 2 and beyond)**				
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 2**	**Cycle 1 Day 15**	**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Tumor and PROs FUP**	**End of post treatment FUP**
Visit Numbers[1]	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**
Days	**-**	**-28 to -1**	**Day 1**	**2**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
Localized Bone X-Ray, CT or MRI		X For skeletal abnormalities identified by bone scan at screening				X If skeletal abnormalities present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated	X EOT scan not required if previous scan was performed ≤ 28 days		X If skeletal abnormalities present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated	
Skin Color Photography		X If skin lesions are present				X If skin lesion present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated	X EOT scan not required if previous scan was performed ≤ 28 days		X If skin lesion present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated	

Period	**Screening**		**Treatment: Capmatinib and osimertinib**				**EOT**	**Follow-up**		
Cycle			**Cycle 1 (Cycle 1)**			**Cycle 2 (Cycle 2 and beyond)**				
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 2**	**Cycle 1 Day 15**	**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Tumor and PROs FUP**	**End of post treatment FUP**
Visit Numbers[1]	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**
Days	**-**	**-28 to -1**	**Day 1**	**2**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
Electrocardiogram (ECG)[4]		X (≤72 hr before C1D1)	X (multiple time points)		X (multiple time points)	X At C4D1 (2 time points) and then if clinically indicated	X			
Cardiac imaging (MUGA or ECHO)		X (≤15 days before C1D1)				X At C4D1 and then if clinically indicated	X			
Adverse Events		X Continuously from signing of main ICF until 30 days after last dose of study treatment								
Serious Adverse Events	X 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								X SAEs related to study treatment unless otherwise specified by local law/regulations	
Capmatinib and Osimertinib administration			X Capmatinib continuous twice daily dosing [b.i.d.] and Osimertinib continuous once daily dosing [q.d.]							
food consumption[5]			X		X					
PK blood collection (full PK)			X (multiple time points)	X (one time point)	X (multiple time points)					
PK blood collection (Sparse PK)						X (at C3D1 then C4D1 and C6D1 only). Note: for osimertinib at C4D1, two time points will be collected				
Antineoplastic therapies (meds, surgery, radiation) since discontinuation of study drug							X	X	X	X
Disposition		X					X			X

Period	**Screening**		**Treatment: Capmatinib and osimertinib**				**EOT**	**Follow-up**		
Cycle			**Cycle 1 (Cycle 1)**			**Cycle 2 (Cycle 2 and beyond)**				
Visit Name	**Molecular pre-screening**	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 2**	**Cycle 1 Day 15**	**Cycle 2 and beyond**	**EOT**	**30-Day Safety FUP**	**Tumor and PROs FUP**	**End of post treatment FUP**
Visit Numbers[1]	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**
Days	**-**	**-28 to -1**	**Day 1**	**2**	**Day 15**	**Day 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] Visit structure given for internal programming purpose only
[redacted]
[3] By local laboratory
[4] Central ECGs
[5] Capture information of whether capmatinib was administered with or without food.

Table 8-3 Assessment Schedule, Part 2

Period	**Screening**		**Treatment: Both arms: 1-capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
Cycle			**Cycle 1**		**Cycle 2 (and beyond)**		**Cycle 1**	**Cycle 2 (and beyond)**					
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 FUP**	**Tumor and PROs FUP**	**End of post treatment FUP**	**Survival FUP**
Visit Numbers[1]	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**
Days	**-**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**-**	**Day 1**	**Day 1**	**-**	**-**	**-**	**-**	**Every 12 weeks**
Informed consent for molecular pre-screening	X												
[redacted]													

Period	Screening	Treatment: Both arms: 1-capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm	EOT	Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib	ET EOT	Follow-up
[redacted]						

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
[redacted]													
IRT pre-screening registration	X												
Inclusion / Exclusion criteria	X	X											
IRT eligibility check		S											
IRT registration		X	X		X	X	X	X	X				
Main informed consent[14]		X											
Informed consent for treatment beyond progression			X (Participants who meet the criteria outlined in Section 6.1.5.1)				X (Participants who meet the criteria outlined in Section 6.1.5.1)						
Demography	X												

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
Medical history/current medical conditions		X											
Diagnosis and stage of cancer	X												
Smoking history		X											
Prior antineoplastic therapy (meds, surgery, radiation)		X											
Prior/concomitant medications		X Continuously from 28 days prior to first dose until 30 days after last dose of study treatment									X[3,4]		
IRT randomization			X										
Physical examination, including neurological exams		S	As clinically indicated										
Targeted physical examination			S	S	S	S	S	S	S				
ECOG performance status		X	X		X	X	X	X	X		X[3]		
Body Height		X											
Body Weight		X	X	X	X	X	X	X	X				
Vital Signs		X	X	X	X	X	X	X	X				

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
HIV history (HIV testing where locally required)		S											
Hematology[5]		X (≤ 72 hr before C1D1)	X	X	X	X	X	X	X				
Clinical chemistry[5]		X (≤ 72 hr before C1D1)	X	X	X	X	X	X	X				
Coagulation panel[5]		X (≤ 72 hr before C1D1)	As clinically indicated										
Urinalysis (dipstick)[6]		X	As clinically indicated										
Pregnancy Test (serum)		S (≤ 72 hr before C1D1)				S			S				
Pregnancy test (urine)					S			S					

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
CT or MRI chest and abdomen		X			X Starting at C3D1 every 6 weeks (+/- 7 days) for the first 18 months after C1D1, then every 12 weeks (+/- 7 days) thereafter until PD determined using RECIST 1.1 by local investigator and confirmed by BIRC	X EOT scan not required if previous scan was performed ≤ 28 days					X		

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
Brain CT or MRI		X			X If brain lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.	X EOT scan not required if previous scan was performed ≤ 28 days					X If brain lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.		

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
CT or MRI of other metastatic sites (e.g., neck)		X (mandated for any metastatic sites not captured by CT/MRI of chest, abdomen, and brain)			X If lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.	X EOT scan not required if previous scan was performed ≤ 28 days					X If lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.		

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
CT or MRI Pelvis		X			X If pelvic lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.	X EOT scan not required if previous scan was performed ≤ 28 days					X If pelvic lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.		
Whole body bone scan		X	If clinically indicated								If clinically indicated		
Localized Bone X-ray, CT or MRI		X If skeletal abnormalities			X If skeletal abnormality is present at screening,	X EOT scan not required if previous					X If skeletal abnormality is		

Period	**Screening**		**Treatment: Both arms: 1-capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
		identified by bone scan at screening			follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.	scan was performed ≤ 28 days					present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.		

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
Skin color photography		X If skin lesions at screening			X If skin lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.	X EOT scan not required if previous scan was performed ≤ 28 days					X If skin lesion is present at screening, follow the same schedule as CT/MRI of the chest and abdomen. Otherwise, only as clinically indicated.		
Electrocardiogram (ECG)[7]		X (≤72 hr before C1D1)			X At C2D1 (2 time points) and then if clinically indicated	X		X At C2D1 (2 time points) and then if clinically indicated	X				
Cardiac imaging (MUGA or ECHO) [7]		X (≤15 days before C1D1)			X At C4D1 and then if clinically indicated	X		X At C4D1 and then if clinically indicated	X				

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
Adverse Events		X Continuously from signing of main ICF until 30 days after last dose of study treatment											
Serious Adverse Events	X 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										X SAEs related to study treatment unless otherwise specified by local law/regulations		
PROs (EORTC QLQ-C30 and EORTC LC13)[8]			X		X Starting at C3D1 and then every 6 weeks for the first 18 months after C1D1, then every 12 weeks thereafter until PD determined using RECIST 1.1 by local investigator and confirmed by BIRC	X (only if EOT is due to PD)		X at 6, 12 and 18 weeks (+/- 7 days) post progression from platinum – pemetrexed based doublet chemotherapy treatment [13]			X (only if EOT is not due to PD)	X (only if EOT is not due to PD)	X For all participants at 6, 12 and 18 weeks (+/- 7 days) post progression[13]

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
PROs (NCCN Fact Brain Symptom Index and EQ-5D-5L)[8]			X		X Starting at C2D1 and then every 6 weeks for the first 18 months after C1D1, then every 12 weeks thereafter until PD determined using RECIST 1.1 by local investigator and confirmed by BIRC	X (only if EOT is due to PD)		X Optional at 6, 12 and 18 weeks (+/- 7 days) post progression from platinum – pemetrexed based doublet chemotherapy treatment [13]			X (only if EOT is not due to PD)	X (only if EOT is not due to PD)	Optional for all participants at 6, 12 and 18 weeks (+/- 7 days) post progression[13]
Capmatinib and Osimertinib administration (arm 1 and ET)			X Capmatinib continuous twice daily dosing [b.i.d.] and Osimertinib continuous once daily dosing [q.d.]				X Capmatinib continuous twice daily dosing [b.i.d.] and Osimertinib continuous once daily dosing [q.d.]						
Platinum-pemetrexed based doublet Chemotherapy (arm 2)			X		X Day 1 for every cycle [9]								
food consumption[10]					X (for C2D1 only)								

Period	**Screening**		**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**			**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**		**ET EOT**	**Follow-up**			
PK blood collection - capmatinib + osimertinib arm			X (Pre-dose samples)		X pre-dose samples (starting at C2D1 then on C3D1, C4D1 and C6D1 only). Note: for C2D1, three time points will be collected for capmatinib and osimertinib separately (1 pre-dose and 2 post-dose)								
Antineoplastic therapies (meds, surgery, radiation) since discontinuation of study drug						X			X	X	X	X	X
Disposition		X				X			X			X	
Survival (survival information can be obtained via telephone contact)													X
Trial Feedback Questionnaire[11]			S		S (at Cycle 4 Day 1 only)	S							

Period	**Screening**	**Treatment: Both arms: 1- capmatinib and osimertinib arm and 2- platinum-pemetrexed based doublet chemotherapy arm**	**EOT**	**Extension Treatment (ET) for platinum-pemetrexed based doublet chemotherapy participants who crossover to receive capmatinib+osimertinib**	**ET EOT**	**Follow-up**

[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] Visit structure given for internal programming purpose only
[redacted]
[3] Only for participants with brain metastases at baseline
[4] Steroids collection only
[5] By Central laboratory for treatment arms 1 and 2 (except for China: local laboratory allowed); by local laboratory for ET
[6] Optional assessment for China only
[7] Central ECGs and Cardiac Imaging: applicable for all participants at screening and if clinically indicated. ECGs at C2D1 and Cardiac Imaging at C4D1 and EOT are applicable only for participants randomized into capmatinib + osimertinib arm (including ET phase). For ET, an uscheduled ECG will be used as baseline ECG.
[8] During treatment and efficacy follow-up period, questionnaires could be performed either at home on own patient device (within 3 days before the scheduled visit) or on site on the day of the scheduled visit before performance of any assessment. For post-progression timepoints, for participant who might not return to the clinic, PRO completion can be done either at home on own patient device, or by interview (refer to Section 8.5.1)
[9] Participants whose disease has not progressed after four cycles of platinum-based chemotherapy may receive pemetrexed monotherapy maintenance therapy (pemetrexed 500 mg/m^2 on Day 1 of every 21 days cycle).
[10] Capture information of whether capmatinib was administered with or without food.
[11] The trial feedback questionnaires are optional.
[redacted]
[13] For participants who crossed over to ET, PROs will be collected only post – platinum – pemetrexed based doublet chemotherapy progression. These assessments do not have to be performed during survival follow-up if done during ET.
[14] Participants who crossover to ET must be consented under ICF related to Protocol Amendment 02

8.1 Screening

Molecular Pre-screening

In order to be considered eligible for the study, participants must have written documentation of EGFR activating mutation and, for participants previously treated with 1st or 2nd generation EGFR TKIs, or other 3rd generation EGFR TKI other than osimertinib, must also have tissue EGFR T790M negative test results (see Section 5.1). The results from CLIA-certified USA laboratory or an accredited local laboratory for sites outside of the USA, using a validated test, according to local regulations (prior to enrolling in the trial) will satisfy the EGFR status-related inclusion criteria. For the randomized part, if T790M testing is not available locally, a tissue-based confirmation of negative T790M status at the Novartis-designated central laboratory for patients who have progressed on 1st or 2nd generation EGFR TKI or 3rd generation EGFR TKI other than osimertinib will be needed. In this case, the tumor and blood samples are collected for central T790M testing and should be indicated in the appropriate eCRF and requisition forms.

A blood T790M negative test result is not required for eligibility; however participants with known T790M positive tissue or blood status are excluded from the study.

Participants previously treated with osimertinib do not require mandatory confirmation of EGFR T790M negative status, however participants with known T790M positive status are excluded from the study.

Part 1

For run-in part, participants must be enrolled based on local result for MET amplification status by either tissue or blood. A tumor tissue biopsy and a blood sample will need to be sent for retrospective analysis and may also be used toward the development of an *in vitro* diagnostic test, such as a companion diagnostic.

Part 2

For the randomized part, eligible participants must have MET amplification confirmed by a Novartis designated central laboratory prior to randomization. MET amplification will be identified using a central FISH test that detects MET amplification via Deoxyribonucleic Acid (DNA) derived from formalin fixed, paraffin-embedded human tissue. The central MET amplification test is investigational and is being clinically validated for selecting patients most likely to benefit from capmatinib as a part of this study. The test is sufficiently validated for the purposes of selecting participants with MET amplification in their NSCLC tumor sample.

If a participant's MET amplification status is known via a local result by tissue or blood, participant may commence screening following signature of the main ICF. However, confirmation by a Novartis-designated central laboratory is required to confirm eligibility prior to randomization. The pre-screening results from central testing for all tested participants (whether the participant is eligible or not for the study) will be communicated to the respective study center by the Novartis-designated central laboratory.

For both study parts

The biopsy sample for MET amplification testing should be performed during or after disease progression on prior EGFR TKI therapy is observed (either clinically or radiologically). MET testing may be performed while participants are still receiving anti-cancer therapy as long as progression on prior EGFR TKI therapy was observed prior to biopsy. The participant can only start study therapy once he/she has discontinued the last prior systemic treatment due to disease progression, as specified in Section 5.2.

All participants will be asked to sign and date an IRB/ IEC approved "Molecular pre-screening informed consent form" before their tumor sample is sent for testing to the Novartis-designated central laboratory. A newly obtained tumor biopsy (preferred) or archival tumor tissue (block or slides) should be submitted for all participants to the Novartis-designated laboratory to test for MET amplification status and, where applicable in the randomized part only, for EGFR T790M testing. The archival tumor tissue must have been obtained after progression on prior line of EGFR TKI. If more than one archival tissue sample post EGFR TKI progression is available, tissue from the most recent biopsy is preferred. Samples obtained from bone metastases and cytology samples are not acceptable. Additionally, a blood sample (2 x 10 mL) will be collected at Pre-Screening for potential use towards the development of a liquid biopsy *in vitro* diagnostic test, such as a companion diagnostic.

If a tumor block or newly obtained biopsy is provided, the remaining tissue from pre-screen or screen failure samples will be returned to the site. However, a small amount of any remaining tissue will be retained from all participants, under control of Novartis, to support the potential development of an *in vitro* diagnostic test(s), such as a companion diagnostic test(s) with a method such as NGS, FISH, or PCR. If the participant is enrolled, the remaining block will be sent to the Novartis-designated vendor. [redacted] Additional tissue may be requested, retrospectively, if available, to support potential development of companion diagnostic test(s) if the remaining tissue sample is insufficient for analysis.

The sample collection information must be entered on the appropriate sample collection log eCRF page(s) and requisition form(s). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in a separate Laboratory Manual.

Participants who crossover to capmatinib + osimertinib treatment do not have to re-confirm eligibility regarding their molecular testing.

Main screening

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

Participants will be evaluated against study inclusion and exclusion criteria and safety assessments (refer to Table 8-2 and Table 8-3). Screening assessments must be repeated if

performed outside of the specified screening window (Table 8-1). Participants must meet all inclusion and none of the exclusion criteria at screening in order to be eligible for the study.

Laboratory assessments performed as part of the screening evaluations will not be required to be repeated prior to dosing (except hematology/chemistry and serum pregnancy test if not done within 72 hours prior to treatment start) unless deemed clinically necessary by the investigator and/or required as per local institutional policies. Laboratory test result(s) or symptoms that do not satisfy the eligibility criteria may be repeated or treated during the screening visit window. In the event that the repeated laboratory test(s) cannot be performed within 28 days from the original screening visit, or do not meet the eligibility criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screening failure.

Re-screening of a participant who has failed screening may be allowed. In such cases, a new ICF must be signed. A new participant number will be assigned to the participant.

All required screening assessments must be repeated if they do not meet the allowed time window for screening when the participant is re-screened for participation in the study. Samples already collected for pre-screening visit are not required to be re-collected in case of re-screening. An individual participant can only be re-screened once for the study.

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

Participants who are screened and eligibility confirmed in IRT system, but fail to start treatment, e.g., participants confirmed in IRT in error, will be considered as early terminations. The reason for early termination should be recorded on the appropriate eCRF.

8.1.1 Eligibility screening

When all screening procedures are completed and once the participant's eligibility has been checked and confirmed (i.e., all inclusion/exclusion criteria have been verified), the key eligibility criteria checklist will be completed prior to the first dose of study treatment in the IRT system by the investigator or designee. The eligibility check will be embedded in the IRT system. Please refer to Section 6.3.2 for further details on treatment assignment/randomization as well as comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

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

The following eCRF pages must be completed for screening failure 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 serious adverse event (SAE) during the screening phase (see SAE section for reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported (i.e., tumor biopsy collection) will be reported to the Novartis Safety group.

The IRT must be notified within 2 days of the screen fail.

For Run-in Part: participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition eCRF.

For Randomized Part 2: participants who are randomized and fail to start treatment, i.e., participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Participant demographics/other baseline characteristics

Data to be collected on participant characteristics at screening include:

- Demography (age, gender, race and ethnicity, or as allowed by local regulations). Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities
- Other background or relevant medical history (including smoking history) / (serious) adverse events
- Cancer characteristics including diagnosis, history, extent of cancer, baseline tumor mutation / amplification / protein expression status (EGFR, T790M, MET and PD-L1), prior antineoplastic therapies (medications, radiation, surgeries), and date of progression prior to study entry
- Tumor imaging assessments
- Other assessments to be completed for the purpose of determining eligibility (ECOG PS, complete physical examination, vital signs, hematology, blood chemistry, coagulation studies, urinalysis, HIV testing where locally required [only recorded in source documentation], serum pregnancy test for women of child-bearing potential [only recorded in source documentation], 12-Lead ECG and Cardiac Imaging)

- Prior and current concomitant medications and surgical and medical procedures

Data to be collected on C1D1 pre-dose include:

- Patient Reported Outcomes (PROs) (applicable only for randomized part).

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

8.3 Efficacy

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

8.3.1 Tumor imaging assessment

Participants should have at least one documented measurable lesion at study entry as per RECIST 1.1. The imaging assessment collection plan is presented in Table 8-4.

For part 1 (run-in part): tumor response will be assessed locally only, according to the Novartis guideline version 3.2 (Section 16.1) based on RECIST 1.1 (Eisenhauer et al 2009).

For part 2 (randomized part): tumor response will be assessed locally and centrally according to the Novartis guideline version 3.2 (Section 16.1) based on RECIST 1.1 (Eisenhauer et al 2009). In addition, CNS lesions will be assessed by BIRC based on Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria Novartis guidelines (Section 16.2).

The central review of the scans will be carried out in a blinded fashion. Further details of the central review process will be described in the BIRC charter.

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The results of the central evaluations will be used for primary analysis and secondary analysis purposes of the randomized part. The local investigator's assessment will be used for the supportive analysis and for treatment decision making. Details regarding collection and shipment of additional information required for imaging assessment including RANO-BM assessment by BIRC will be described in the imaging manual provided by the designated CRO.

Table 8-4 Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest and abdomen CT or Magnetic Resonance Imaging MRI (with intravenous contrast enhancement)	Mandated	Mandated **Starting at C3D1**: every 6 weeks (+/- 7 days) for the first 18 months after C1D1, then every 12 weeks (+/- 7 days) thereafter until PD determined using RECIST 1.1 by investigator (run-in part) or by investigator and confirmed by BIRC (randomized part)

Procedure	Screening/Baseline	During Treatment/Follow-up
		At End of Treatment if not done within 28 days. **Post Treatment Follow-Up:** participants with EOT reason other than disease progression, withdrawal of consent, opposition to use data or death will continue collect imaging and follow the same schedule of every 6 weeks (+/- 7 days) for the first 18 months after C1D1, then every 12 weeks (+/- 7 days) thereafter until PD determined using RECIST 1.1 by investigator (run-in part) or by investigator and confirmed by BIRC (randomized part).
Pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Only if lesions were documented at baseline or if clinically indicated; follow the same schedule as CT/MRI of chest and abdomen
Brain CT or MRI (with intravenous contrast enhancement)	Mandated	Only if lesions were documented at baseline or if clinically indicated; follow the same schedule as CT/MRI of chest and abdomen.
Whole body bone scan (Per institutional standard of care [e.g., Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride (NaF) PET])	Mandated	If clinically indicated
Localized bone CT, MRI, or x-ray	Mandated for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	Only if lesions were documented at baseline or if clinically indicated; follow the same schedule as CT/MRI of chest and abdomen
Skin color photography (with scale/ruler)	Mandated for any skin lesions present	Only if lesions were documented at baseline or if clinically indicated; follow the same schedule as CT/MRI of chest and abdomen
CT or MRI of other metastatic sites (e.g., neck)	If other metastatic sites are suspected	Only if lesions were documented at baseline or if clinically indicated; follow the same schedule as CT/MRI of chest and abdomen

8.3.1.1 Baseline imaging assessment

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1) as per Table 8-2, Table 8-3 and Table 8-4.

Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to start of treatments for the whole body bone scan, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images.

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

Contrast enhanced brain MRI must be completed for all participants unless MRI contrast is contraindicated. If MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

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

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

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

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of i.v. contrast media. At the discretion of the investigators, FDG-PET scans may be performed to document PD per RECIST 1.1 (Section 16.1).

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

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

8.3.1.2 Post-baseline imaging assessment

Imaging assessments as described in Table 8-4 should be performed at the time points specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 8-1). Imaging assessments for response evaluation will be performed starting at C3D1 every 6 weeks (+/- 7 days) for the first 18 months after C1D1, then every 12 weeks (+/- 7 days) thereafter until disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples. Imaging assessments should be scheduled using the date of first dose of study treatment as the reference date (not the date of the previous tumor assessment) and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed. If an unscheduled imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule. Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a participant, as necessary.

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

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent.

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

If participants start on a new antineoplastic therapy before documented progression, every effort should be made to continue to collect tumor assessment according to the planned schedule.

8.3.1.3 Confirmation of disease progression (for randomized part only)

Time points at which progression is determined locally

All participants who have disease progression determined by the local investigator require an expedited central review. Rapid image transmission to the imaging CRO may be accomplished by transferring the images electronically, e.g., via the Internet. In all instances, the process at the imaging CRO will ensure that the central reviewers remain blinded to the results of the local assessment and the expedited nature of the review. The investigator seeking an expedited review must indicate this request to the imaging CRO on a designated form or by alternative means. Further details of the central review process will be described in the BIRC charter.

The imaging will undergo expedited central review (within 5 business days from the time of image receipt at the imaging CRO and once all applicable queries are resolved**)** and the results of the central review will be communicated to the site. While the investigator is awaiting the results of the central review, it is preferable that the participant continue on study treatment.

However, during this time, the investigator should do whatever is medically necessary for his/her participant.

If the central review determines disease progression, then the participant will discontinue study treatment and subsequent tumor assessments are no longer required (not applicable to treatment beyond disease progression. Refer to Section 6.1.5.1).

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

Participants will continue to have imaging performed as per protocol (Table 8-4) until the central review determines disease progression.

Time points without locally determined progression

All imaging time points without locally determined progression will be read on an ongoing, non-expedited basis as detailed in the imaging manual to be provided by the designated imaging

CRO and independent review charter. Results of these readings will not be communicated to the sites.

For participants who crossover to capmatinib in combination with osimertinib treatment, the disease progression will be determined based on investigator assessment only. Imaging assessment should be performed according to local practice and institutional guidelines. Reason for discontinuation and date of disease progression will be captured in the eCRF.

Treatment beyond disease progression

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

8.3.1.3.1 Progression on next line of therapy (PFS2) - applicable to both Run-In and Randomized parts

For PFS2, the disease progression will be determined based on investigator assessment of progression on next-line therapy. For this purpose, subsequent antineoplastic therapies including start/end date, reason for discontinuation and date of disease progression will be captured in the appropriate eCRF.

8.3.1.4 Efficacy Follow-up Imaging Assessment - applicable to both run-in and randomized parts

For participants who discontinue treatment for reasons other than initial disease progression as per RECIST 1.1 (either by investigator assessment - run-in part - or by investigator and BIRC assessement - randomized part-), tumor assessments must continue to be performed as outlined in Table 8-2 and Table 8-3, regardless if participants start on new antineoplastic therapy before documented disease progression. Please refer to Section 9.2 for additional information.

8.3.2 Appropriateness of efficacy assessments

Tumor assessments every 6-12 weeks of chemotherapy are consistent with the standard clinical practice. Different guidelines for advanced NSCLC recommend response assessment every 6-12 weeks after first line therapy.

Based on available data (Mok et al 2017) and the negative prognostic impact of the MET dysregulation and T790M negative population, the median PFS in the control arm (platinum - pemetrexed based doublet chemotherapy) is expected to be around 4.5 months or 18 weeks. Conducting tumor evaluations more than 6 weeks apart may expose a participant to an unnecessary treatment if the disease progression event takes place between the infrequent assessments or prevent from early identification of progression lesions and appropriate treatment.

8.3.3 Overall survival

Run-in part:

Survival follow-up is not applicable

Randomized part:

All participants will enter the survival follow-up period once they complete the safety follow-up and efficacy follow-up after treatment discontinuation (whichever is longer). Survival status will be collected every 12 weeks (+/- 14 days) regardless of treatment discontinuation reason (except if consent is withdrawn or participant is lost to follow-up) until death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples for survival follow-up.

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

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

8.4 Safety

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, the method of collection of safety assessments may be modified. See Section 10 for more details.

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

Table 8-5 Physical Assessments

Assessments	Specification
Physical examination	Significant findings that were present prior to the signing of informed consent must be included as medical history on the participant's eCRF. Significant new findings that begin or worsen after informed consent must be recorded as an adverse event on the appropriate eCRF. **Physical examination** At screening, a complete physical examination will be performed including the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological systems. More frequent examinations may be performed at the discretion of the investigator and if medically indicated. Information about the physical examination must be present in the source documentation. **Targeted physical examination** A targeted physical exam will be performed at all visits as indicated in Table 8-2 and Table 8-3 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 exams will be performed.

Assessments	Specification
	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.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, repiratory rate, and body temperature. They will be measured at screening and at subsequent time points as specified in Table 8-2 and Table 8-3.
Height and weight	Height will be measured at screening. Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-2 and Table 8-3.
Performance status	The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale as specified in Table 8-6 following the schedule given in Table 8-2 and Table 8-3.

Table 8-6 ECOG Performance Status

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

8.4.1 Laboratory evaluations

For the run-in part, no central laboratory will be used - All laboratory analysis will be performed locally, inclusive of assessment for participants' eligibility.

For the randomized part: a central laboratory will be used for analysis of all specimens collected, except urinalysis, pregnancy testing and HIV testing (where locally required), which will be performed locally. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the *[Laboratory Manual]*. For China only, local laboratories can be used for all specimens collected (ie: central laboratory assessments not mandatory).

For the ET part: no central laboratory will be used. All laboratory analysis will be perfomed locally.

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

In case of off-site visits, samples that can be collected remotely will be collected and analyzed in line with the [Laboratory Manual].

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

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

For assessment of participants' eligibility to the randomized part of study, only laboratory results from the central laboratory will be used. Clinically significant abnormalities must be recorded as either medical history / current medical conditions or adverse events as appropriate.

Table 8-7 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells, Red blood cells, Differential [Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands*, Other. Absolute value preferred, %s are acceptable unless indicated otherwise]
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Calcium, Magnesium, Phosphate, Sodium, Potassium, Creatinine, Creatine kinase, Creatinine Clearance, Total Bilirubin, Direct Bilirubin (only if total bilirubin is ≥ grade 2), Blood Urea Nitrogen (BUN) or Urea Amylase, Lipase, Glucose (fasting) (non-fasting allowed post-baseline) Bicarbonate, Chloride, Uric Acid at screening and thereafter if clinically indicated
Urinalysis	Local laboratory: Macroscopic Panel (Dipstick)* (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If dipstick is abnormal then perform local laboratory Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or Quick Test (QT), International normalized ratio [INR]),
Pregnancy Test	At screening (and/or Cycle 1 Day 1) a serum pregnancy test is to be performed within 72 hr before the first dose, while during the study (Day 1 of each cycle) urine pregnancy tests are sufficient. An End of Treatment serum pregnancy test is also required to be performed. For women considered to be post-menopausal and not of child-bearing potential, pregnancy testing is not required. If a serum pregnancy test is required as per local practice at day 1 of every cycle, the urine pregnancy test does not need to be repeated.
Infection markers	HIV testing (where locally required)
* Assessements are optional for China only	

8.4.1.1 Hematology

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

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

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

8.4.1.2 Clinical chemistry

Clinical chemistry tests are to be performed according to the visit schedule outlined in Table 8-2 and Table 8-3.

For details of the biochemistry panel see Table 8-7. Biochemistry should be assessed on the actual scheduled day, even if study treatment is being withheld.

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

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

8.4.1.3 Urinalysis

Urinalysis Dipstick measurements will be performed as per Table 8-7 and according to the schedule of assessments (Table 8-2 and Table 8-3). Any significant findings on dipstick will be followed up with microscopic evaluation.

8.4.1.4 Coagulation

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

8.4.2 Electrocardiogram (ECG)

In both parts (run-in and randomized part, including ET), ECGs will be evaluated centrally.

Triplicate 12 lead ECGs are to be collected with ECG machines supplied by the central ECG laboratory. ECGs will be performed at the time points indicated in Central ECG collection plan (Table 8-8 and Table 8-9).

For participants who crossover to ET, an unscheduled ECG has to be performed within 3 days prior to ET-C1D1 which will serve as baseline ECG.

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

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

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

Any identifier details must be redacted e.g., subject initials, date of birth, where local regulations require it.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms), a copy of the assessment is sent to the central ECG laboratory for expedited review, and the ECG is repeated to confirm the diagnosis. If the participant is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion). In

case of off-site visits, ECGs will be recorded remotely and transmitted electronically or in paper version to the central ECG laboratory, in line with instructions included in the protocol.

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

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate eCRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site.

Clinically significant findings must be discussed with Novartis prior to dosing (run-in part) or randomizing the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Clinically significant ECG abnormalities present at screening should be reported on the appropriate CRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

All ECGs must be recorded using the machines supported by the central ECG laboratory and transmitted electronically to the central ECG laboratory to be centrally reviewed by an independent reviewer. Any original ECG not transmitted electronically to the central ECG laboratory should be forwarded for central review.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated, and transmitted electronically to the central ECG laboratory as unscheduled timepoints. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central ECG laboratory for review.

The results of the centrally assessed ECGs are automatically transferred into the clinical database.

Table 8-8 Central ECG (run-in part) collection plan

Cycle	Day	Time	ECG Type
Screening		Anytime (≤ 72 hr before C1D1)	12 Lead, triplicate
1	1	Pre-dose Post-dose 2 h (within 15 min prior to PK) Post-dose 4 h (within 15 min prior to PK) Post-dose 6 h (within 15 min prior to PK) Post-dose 8 h (within 15 min prior to PK)	12 Lead, triplicate
1	15	Pre-dose Post-dose 2 h (within 15 min prior to PK)	12 Lead, triplicate

Cycle	**Day**	**Time**	**ECG Type**
Screening		Anytime (≤ 72 hr before C1D1)	12 Lead, triplicate
		Post-dose 4 h (within 15 min prior to PK) Post-dose 6 h (within 15 min prior to PK) Post-dose 8 h (within 15 min prior to PK)	
4	1	Pre-dose (within 15 min prior to PK)	12 Lead, triplicate
		Post-dose 6 h (within 15 min prior to PK)	
EOT		Anytime	12 Lead, triplicate
Unscheduled ECG		Anytime if clinically indicated	12 Lead, triplicate

Table 8-9 Central ECG (randomized part and ET part) collection plan

Cycle	Day	Time	ECG Type
Screening (applies for all participants)		Anytime (≤ 72 hr before C1D1)	12 Lead, triplicate
2 (applies only for participants randomized into the capmatinib + osimertinib arm and participants who crossover to ET)	1	Pre-dose (within 15 min prior to PK*)	12 Lead, triplicate
		Post-dose 6 h (within 15 min prior to PK*)	
EOT (applies only for participants randomized into the capmatinib + osimertinib arm and participants who crossover to ET)		Anytime	12 Lead, triplicate
Unscheduled ECG (applies for all participants) **		Anytime if clinically indicated	12 Lead, triplicate
* In ET, ECGs will be collected without PK sample collection ** An uscheduled ECG which will serve as baseline ECG is required for participants who crossover to ET within 3 days prior to ET-C1D1			

8.4.2.1 MUGA (multiple gated acquisition) scan or echocardiogram

An Echocardiogram or MUGA scan to assess LVEF will be performed at screening (within 15 days prior to study medication/C1D1), at C4D1 (only for participants in the capmatinib + osimertinib arm, including ET), and as clinically indicated, and at end of treatment visit (only for participants in the capmatinib + osimertinib arm, including ET).

In the run-in and randomization parts, assessment will be performed locally. The modality of the cardiac function assessments must be consistent throughout ie, if echocardiogram is used for the screening assessment then echocardiogram should also be used for subsequent scans. The participant should also be examined using the same machine and operator whenever possible.

8.4.3 Pregnancy and assessments of fertility

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

All women of child-bearing potential will have a serum pregnancy test within 72 hours prior to the first dose of study treatment. hCG may also be considered a tumor marker, therefore if hCG levels are detected, another blood sample at least 4 days later must be taken to assess the kinetics of the increase, and a transvaginal ultrasound must be performed to rule out pregnancy. Urine pregnancy tests will be required to be performed on Day 1 of every cycle beginning with Cycle 2, followed by serum pregnancy test at the end of treatment visit. Women of child-bearing potential will be instructed to contact the site immediately at any time during the study (on-treatment or during follow-up) should they have a positive pregnancy test.

In case of positive urine pregnancy testing, additional testing must be performed to confirm the pregnancy, and, if confirmed, follow the reporting requirements as described in Section 10.1.4.

A positive pregnancy test requires immediate discontinuation of study treatment. If a positive pregnancy test is performed in between study visits, the participant must immediately notify the investigator. Male participants must notify the investigator in case their partner is confirmed with positive pregnancy test results during the treatment period. See Section 10.1.4 for pregnancy reporting.

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

If participants cannot visit the site to have serum pregnancy tests 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, 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.

8.4.3.1 Assessment of fertility

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

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

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

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

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO) (Randomization part only)

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

This study will implement the following PROs:

- The European Organization for Research and Treatment of Cancer's core quality of life questionnaire EORTC (QLQ-C30)
- The Lung Cancer module of the EORTC's quality of life questionnaire EORTC (QLQ-LC13)
- NCCN FACT-Brain Symptom Index version 2.0 (FBrSI)
- The EuroQoL 5-level instrument (EQ-5D-5L, tablet version)

The EORTC QLQ-C30 and QLQ-LC13 are frequently used in clinical trials of participants with advanced or metastatic lung cancer (Aaronson et al 1993, Bergman et al 1994).

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients which has been translated and validated into 81 languages and has been used in more than 3,000 studies worldwide. The questionnaire contains 30 items and is composed of both multi-item scales and single-item measures based on the patients experience over the past week. These include five scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology/problems. All scoring will follow the scoring procedures defined by the EORTC Scoring Manual (Aaronson et al 1993, Fayers 2001).

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

The NCCN FACT-Brain Symptom Index version 2.0 (FBrSI) symptom module will be used to explore changes in symptoms associated with potential BM in this study. The FBrSI was adapted from the previously developed FACT-Brain module. The symptoms module contains 12 items with a recall period of the past 7 days. The participant responds to 12 statements and indicates to what extent it applies to them on a 5-point Likert response scale from "not at all" to "very much." (Lai et al 2014). The 24 statements address three sub-scales: disease related symptoms (which includes 12 physical symptoms and 5 emotional symptoms), treatment side effects (5 items), and function/well-being (2 items).

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

During treatment period and efficacy follow-up period, PRO questionnaires will be collected by self-report using electronic devices. Participants may also be given the possibility to complete PRO questionnaires at home on their own device before arriving at the site on scheduled visit days. Completion at home must be performed within 3 days before the scheduled visit (for more details, refer to vendor manual).

For post-progression timepoints, for participant who might not return to the clinic, PRO completion can be done either at home on own patient device, or by interview over the phone provided the interviewer has received the appropriate training on recordingthe participant's responses.

All PRO assessments should be administered in the participant's most familiar language and according to the visit schedule in Table 8-3, prior to any tests, treatments or receipt of results from any test to avoid biasing the participant's perspective.

The EORTC QLQ C-30 and LC-13 questionnaires should be completed on Cycle 1 Day 1 (or within 3 days prior to this visit), Cycle 3 Day 1 (- 3 days), then every 6 weeks (- 3 days) for the first 18 months after C1D1 and every 12 weeks (- 3 days) thereafter, until End of Treatment (EOT) visit. For the other two PRO questionnaires, following the first administration, they will be completed at alternate visits i.e., the NCCN FACT Brain Symptom Index and EQ-5D-5L questionnaires should be completed on Cycle Day 1 (or within 3 days prior to this visit), Cycle 2 Day 1 (-3 days) then very 6 weeks (-3 days) for the first 18 months after C1D1 and every 12 weeks (-3 days) therafter, until End of treatment (EOT) Visit. Following this:

- for participants who discontinued treatment due to BIRC-Confirmed RECIST 1.1 defined progression and enter the safety survival follow-up period, PROs (all four set of questions) will be collected at EOT (+/- 7 days) and at 6, 12 and 18 weeks (+/- 7 days) post progression.
- for participants who discontinued treatment for any other reason than BIRC-Confirmed RECIST 1.1 defined progression and enter the efficacy follow-up period, PROs will be collected at the same timepoints as imaging assessments until BIRC-Confirmed RECIST 1.1 progression. Following progression, PROs will then be collected within 7 days of the progression and again at 6, 12 and 18 weeks (+/- 7 days) post progression.
- during the survival follow-up period, the NCCN FACT Brain Symptom Index and EQ-5D-5L questionnaires are optional.

For participants who discontinue platinum – pemetrexed based doublet chemotherapy treatment and enter extension treatment, PROs will be collected at 6, 12 and 18 weeks (± 7 days) post-chemotherapy treatment progression only. These assessments do not have to be performed during survival follow-up if done during ET.

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

The participant must be given the PRO measure(s) to be completed at the scheduled visit (if not completed at home on own patient device) before any clinical assessments are conducted and should be given sufficient space and time to complete the PRO measure(s).

Participant's refusal to complete all or any part of a PRO measure should not be captured as a protocol deviation.

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

The participant should be made aware that responses of the completed measure(s) are not reviewed by the investigator/ study personnel and that they should report any discomfort, unusual symptoms or medical problems directly to the Investigator/ study personnel.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, participants could complete the questionnaires at home on their own device or study site staff may administer the questionnaires to the participants via interview over the phone regardless of the study phase (for more details, refer to the vendor manual).

Trial Feedback

This study is including an optional questionnaire, the "Trial Feedback Questionnaire" for trial participants to provide feedback on their clinical trial experience in adherence to local regulations and guidelines. Individual trial participant responses will not be reviewed by investigators. Responses may be used by Novartis to understand where improvements can be made in the clinical trial process. This questionnaire asks questions about trial experience. It does not ask questions about the trial participant's disease, symptoms, treatment effect, or AEs, and, therefore is not considered as trial data.

8.5.2 Pharmacokinetics

Serial blood samples will be collected from all participants in the run-in and those who are randomized to receive capmatinib and osimertinib to assess plasma PK of capmatinib, osimertinib and osimertinib's active metabolites (AZ5104 and AZ7550). Time points of blood sample collection for run-in part and randomization part are outlined in Table 8-10 to Table 8-13.

No PK samples will be collected in the ET phase.

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

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

8.5.2.1 Pharmacokinetic sampling for run-in part

PK blood samples will be collected for all participants in the run-in part, as outlined in Table 8-10 and Table 8-11. Extensive PK samples will be collected on Cycle 1 Day 1, Cycle 1 Day 2 (only for osimertinib) and Cycle 1 Day 15.

Table 8-10 Pharmacokinetic blood collection log for capmatinib (run-in part)

Cycle	Day	Scheduled Time Point	Dose Reference ID		PK Sample No	Sample Volume (mL)
1	1	Pre-dose (0 hour)	11		101	2
1	1	Post-dose 0.5 h (± 5 min)	11		102	2
1	1	Post-dose 1 h (± 10 min)	11		103	2
1	1	Post-dose 2 h (± 15 min)	11		104	2
1	1	Post-dose 3 h (± 15 min)	11		105	2
1	1	Post-dose 4 h (± 20 min)	11		106	2
1	1	Post-dose 6 h (± 30 min)	11		107	2
1	1	Post-dose 8 h (± 60 min)	11		108	2
1	15	Pre-dose	12	121[a]	109	2

Cycle	Day	Scheduled Time Point	Dose Reference ID		PK Sample No	Sample Volume (mL)
1	15	Post-dose 0.5 h (± 5 min)	12		110	2
1	15	Post-dose 1 h (± 10 min)	12		111	2
1	15	Post-dose 2 h (± 15 min)	12		112	2
1	15	Post-dose 3 h (± 15 min)	12		113	2
1	15	Post-dose 4 h (± 20 min)	12		114	2
1	15	Post-dose 6 h (± 30 min)	12		115	2
1	15	Post-dose 8 h (± 60 min)	12		116	2
3	1	Pre-dose	13	131[a]	117	2
4	1	Pre-dose	14	141[a]	118	2
6	1	Pre-dose	15	151[a]	119	2
Unscheduled		Anytime			1001+	2
[a]Dose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample						

Table 8-11 Pharmacokinetic blood collection log for osimertinib, AZ5104 and AZ7550 (run-in part)

Cycle	Day	Scheduled Time Point	Dose Reference ID		PK Sample No	Sample Volume (mL)
1	1	Pre-dose (0 hour)	21		201	3
1	1	Post-dose 0.5 h (± 5 min)	21		202	3
1	1	Post-dose 1 h (± 10 min)	21		203	3
1	1	Post-dose 2 h (± 15 min)	21		204	3
1	1	Post-dose 3 h (± 15 min)	21		205	3
1	1	Post-dose 4 h (± 20 min)	21		206	3
1	1	Post-dose 6 h (± 30 min)	21		207	3
1	1	Post-dose 8 h (± 60 min)	21		208	3
1	2	Post-dose 24 h (± 120 min) / pre-C1D2 am dose	21	211	209	3
1	15	Pre-dose	22	221[a]	210	3

Cycle	Day	Scheduled Time Point	Dose Reference ID		PK Sample No	Sample Volume (mL)
1	15	Post-dose 0.5 h (± 5 min)	22		211	3
1	15	Post-dose 1 h (± 10 min)	22		212	3
1	15	Post-dose 2 h (± 15 min)	22		213	3
1	15	Post-dose 3 h (± 15 min)	22		214	3
1	15	Post-dose 4 h (± 20 min)	22		215	3
1	15	Post-dose 6 h (± 30 min)	22		216	3
1	15	Post-dose 8 h (± 60 min)	22		217	3
3	1	Pre-dose	23	231[a]	218	3
4	1	Pre-dose	24	241[a]	219	3
4	1	Post-dose 6 h (± 30 min)	24		220	3
6	1	Pre-dose	25	251[a]	221	3
Unscheduled		Anytime			2001+	3
[a]Dose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample						

8.5.2.2 Pharmacokinetic sampling for randomization part

PK blood samples will be collected for all participants randomized to the capmatinib plus osimertinib arm as outlined in Table 8-12 and Table 8-13. PK blood samples will not be collected from participants randomized to the platinum-pemetrexed chemotherapy arm.

Table 8-12 Pharmacokinetic blood collection log for capmatinib (randomization part)

Cycle	Day	Scheduled Time Point	Dose Reference ID		PK Sample No	Sample Volume (mL)
1	1	Pre-dose (0 hour)	31		301	2
2	1	Pre-dose	32	321[a]	302	2
2	1	Post-dose 1-4 hours	32		303	2
2	1	Post-dose 6 h (± 30 min)	32		304	2
3	1	Pre-dose	33	331[a]	305	2
4	1	Pre-dose	34	341[a]	306	2
6	1	Pre-dose	35	351[a]	307	2
Unscheduled		Anytime			3001+	2
[a]Dose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample						

Table 8-13 Pharmacokinetic blood collection log for osimertinib, AZ5104 and AZ7550 (randomization part)

Cycle	Day	Scheduled Time Point	Dose Reference ID		PK Sample No	Sample Volume (mL)
1	1	Pre-dose (0 hour)	41		401	3
2	1	Pre-dose	42	421[a]	402	3
2	1	Post-dose 1-4 hours	42		403	3
2	1	Post-dose 6 h (± 30 min)	42		404	3
3	1	Pre-dose	43	431[a]	405	3
4	1	Pre-dose	44	441[a]	406	3
6	1	Pre-dose	45	451[a]	407	3
Unscheduled		Anytime			4001+	3
[a]Dose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample						

8.5.2.3 Pharmacokinetic blood collection and handling

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein at specified time points described in Table 8-10 to Table 8-13.

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

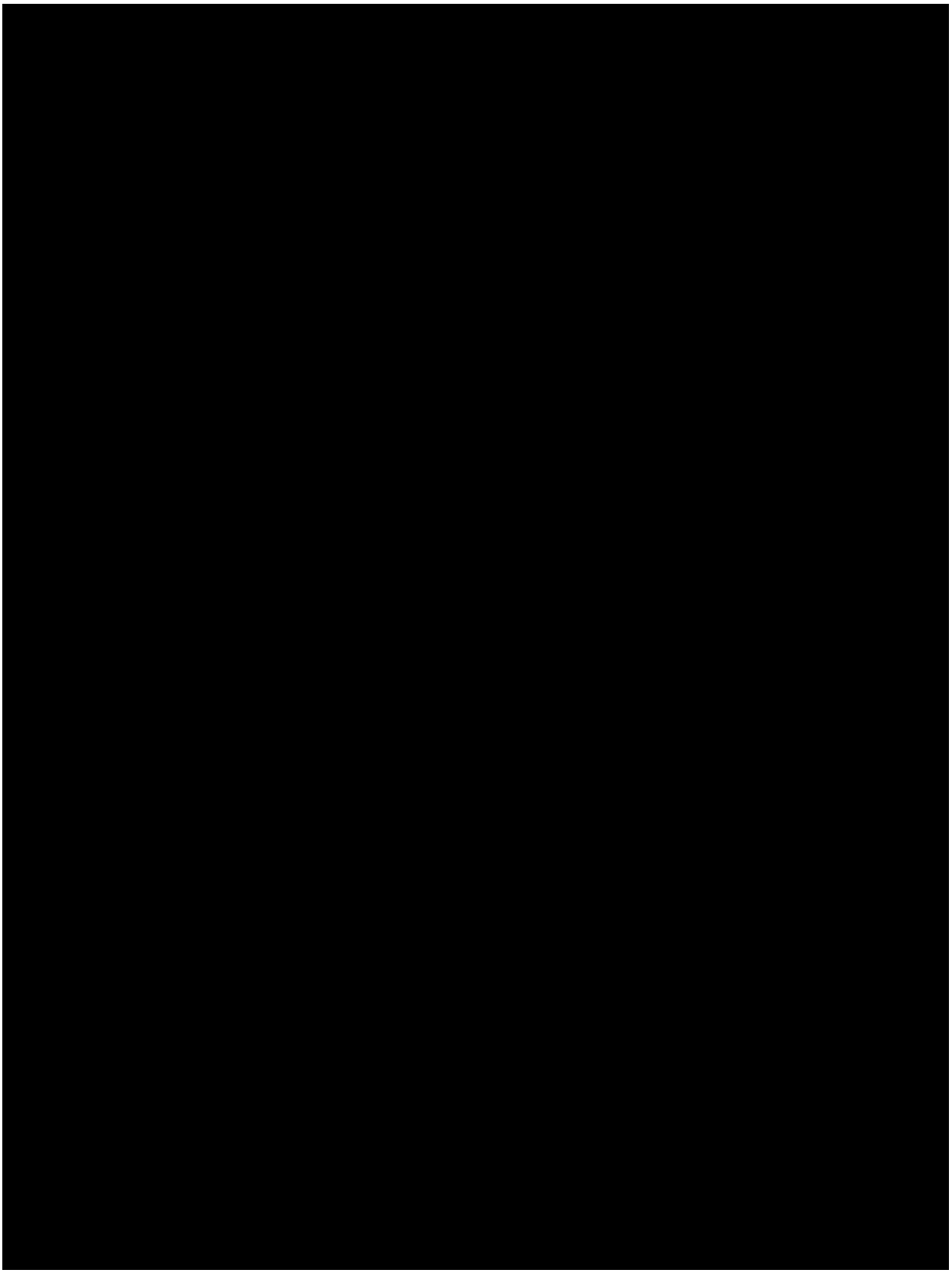
If vomiting occurs within 4 hours following capmatinib administration, post dose PK sample collection is at investigator's discretion. If PK sample collection is done, the clock time of vomiting must be recorded in the dosage administration PK eCRF page.

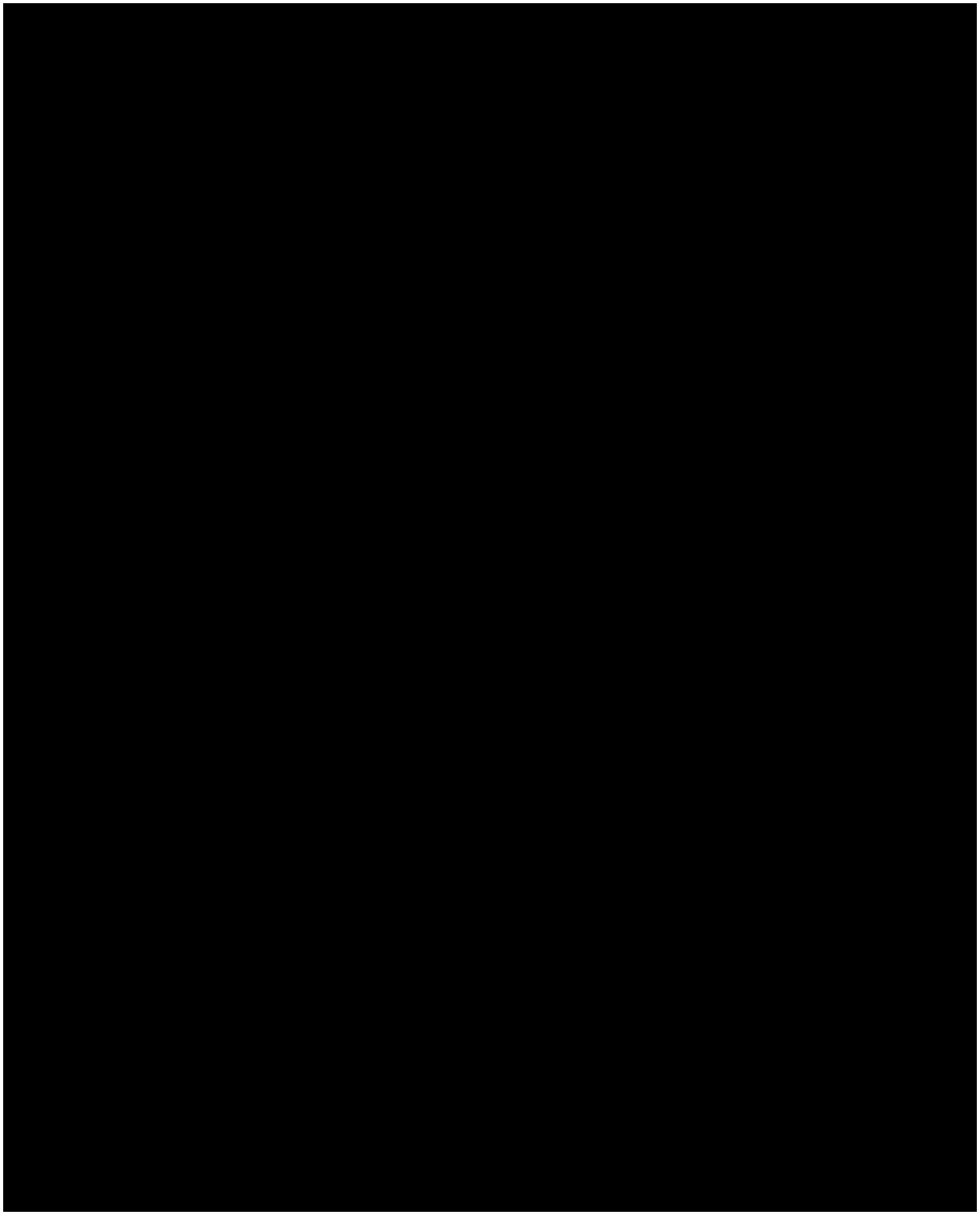
Refer to the *[Laboratory Manual]* for detailed instructions for the collection, handling, and shipment of PK samples.

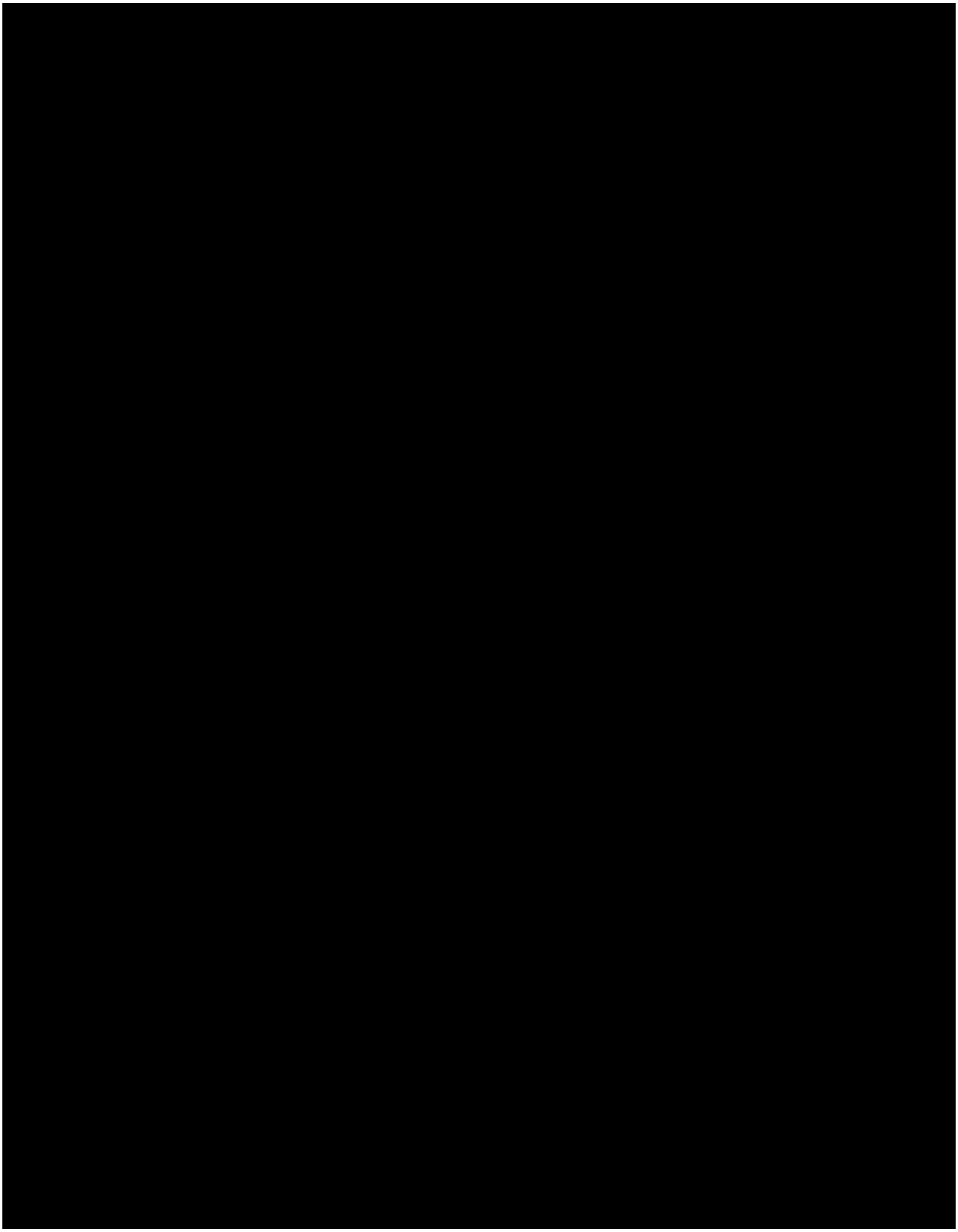
8.5.2.4 Analytical method

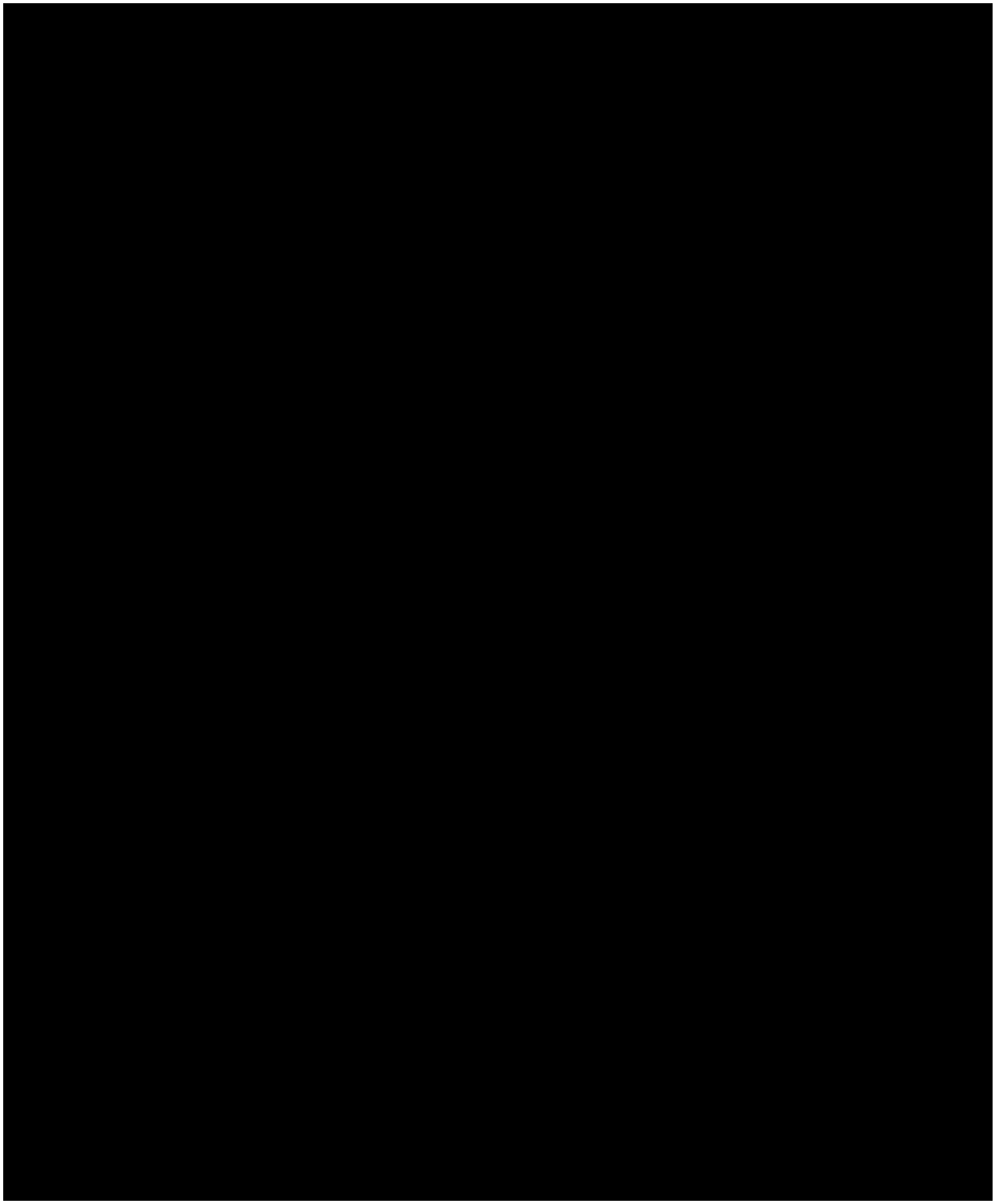
Plasma concentrations of capmatinib, osimertinib, AZ5104, and AZ7550 will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of 1.0 ng/mL, 0.4 ng/mL, 0.4 ng/mL, and 0.4 ng/mL for capmatinib, osimertinib, AZ5104 and AZ7550, respectively, by Novartis Bioanalytics. Concentrations below the LLOQ will be reported as 0.00 ng/mL and missing samples will be labelled accordingly.

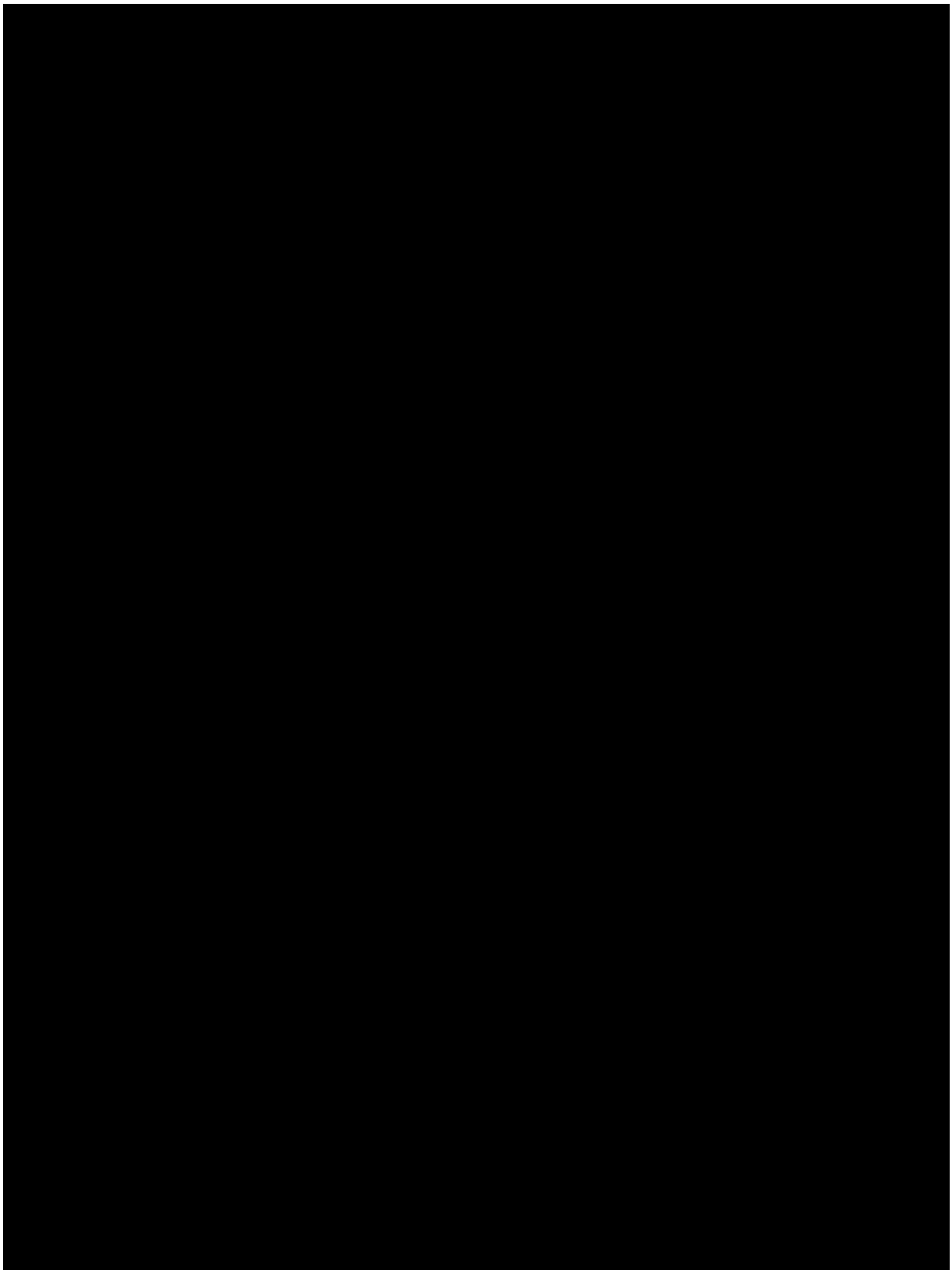
[redacted]











[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Discontinuation from study treatment and from study

Discontinuation from study treatment

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

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

Discontinuation of study treatment is required under the following circumstances:

- Participant/guardian decision
- Investigator decision
- Pregnancy (see Section 10.1.4)
- Any situation in which continued study participation might result in a safety risk to the participant
- Disease progression per RECIST 1.1 (as assessed by the investigator in the run-in part, and as assessed by the investigator confirmed by BIRC in the randomization part). In some circumstances, participants may be allowed to continue to receive study treatment beyond disease progression as per RECIST 1.1. These participants will continue assessments as outlined in Table 8-2 or Table 8-3, as applicable, and will complete the EOT visit only after permanent discontinuation of study treatment (see Section 6.1.4)
- Adverse event requiring permanent discontinuation of study treatment (see Table 6-7)
- Protocol deviation that results in a significant risk to participant's safety

- Withdraw of consent (see Section 9.1.2)
- Study is terminated by the sponsor (see Section 9.1.4)
- Death
- Lost to follow-up

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

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

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

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

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

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

For participants who discontinue from study treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, tumor assessments must continue to be performed every 6 weeks for the first 18 months, then every 12 weeks until documented disease progression per RECIST 1.1 as determined by investigator and confirmed by BIRC, death, lost to follow-up, discontinuation from study or withdrawal of consent/opposition to use data/biological samples.

In some circumstances, participants may be allowed to continue to receive study treatment beyond disease progression as per RECIST 1.1 criteria. These participants will continue assessments as outlined in the assessments section, and will complete the EOT visit only after permanent discontinuation of study treatment.

Discontinuation from study

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

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

9.1.1.1 Replacement policy

Run-in part

Participants will not be replaced on study. However, if a participant is considered as non-evaluable for the Dose-Determination Set (DDS), a new participant will be enrolled until at least the minimum number of 6 evaluable subjects is achieved within each treatment cohort.

Randomized part

No replacements will be needed.

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

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

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

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

This request should be in writing (depending on local regulations) and recorded in the source documentation.

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

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

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

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

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

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

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters,

etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

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 early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued study treatment. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

For individual participant

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

For the study

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

- All participants have discontinued study treatment and completed the safety follow-up and approximately 80% of the participants have died, withdrawn consent or are lost to follow-up.
- Another clinical study becomes available that can continue to provide capmatinib in this participant population, and all participants ongoing are transferred to that clinical study. Note: For participants who transfer to another clinical study or an alternative treatment option to continue provision of study treatment, the follow-up for safety, disease progression and survival will not be performed.

If the primary analysis of PFS does not demonstrate treatment benefit, the follow-up for OS will end, in this case the end of the study will be when all participants have discontinued treatment and completed the safety follow-up, or have withdrawn consent or are lost to follow-up.

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

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

9.2.1 Follow-up for safety evaluations

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

If the participant begins any post-treatment antineoplastic medication before the 30-day safety follow-up period is complete, the collection of new SAEs and AEs unrelated to capmatinib will stop, and, thereafter, only suspected AEs and suspected SAEs will continue to be collected up to day 30. Suspected SAEs will continue to be collected beyond the 30-day safety follow-up. AEs, concomitant medications and antineoplastic therapies since discontinuation of study treatment will be recorded on the appropriate eCRFs during this follow-up period.

9.2.2 Efficacy follow-up and PROs

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

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

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

9.2.3 Survival follow-up

Participants will enter the survival follow-up period once they complete the 30-day safety follow-up and efficacy follow-up (if applicable) after treatment discontinuation (whichever is longer). Participants from randomized part will then be contacted by telephone every 12 weeks to follow-up on their survival status. Any new antineoplastic therapies that have been started since the last contact date will also be collected during these phone calls. At this time, the investigator will record any SAEs that may have occurred after discontinuation of study treatment if the investigator suspects a causal relationship to study treatment.

PRO questionnaires will also be collected in the survival follow-up period at 3 time points (6, 12 and 18 weeks (+/-7 days)) post progression. For participants crossing over to the ET, those three time points (6, 12 and 18 weeks (+/- 7 days)) should be collected during the ET phase.

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

10 Safety monitoring, reporting and committees

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual contact will occur at least every 3 weeks (± 3 days) as per the visit scheduled, or more frequently if needed for safety monitoring and discussion of the participant´s health status until the participant can again visit the site. Events qualifying for being reported in the case report form (i.e., AE, infection) should be entered as appropriate.

If participants can not visit the site to have serum pregnancy tests done, urine pregnancy test kits may be shipped or provided directly to participants (i.e., together with the study drug). Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process will be established with participants so that the site is informed and can verify the pregnancy test results (i.e., following country specific measures).

Depending on local regulations and capabilities, study site staff or Home Nursing Services may visit the participant at home to draw blood/ urine samples if needed. Alternatively, safety lab tests performed locally will be allowed as appropriate.

ECG, echocardiogram or MUGA performed locally (i.e., by the participant´s general practitioner or at another facility) will be allowed as appropriate. Alternatively, depending on local regulations and capabilities, Home Nursing Services or study site staff may visit the participant at home for ECG collection.

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign, including abnormal laboratory findings, symptoms or disease) in a clinical investigation participant after providing written informed consent for participation in the study.

Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

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

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

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered

by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

1. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE V5.0). If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and fatal corresponding to grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.

3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/ not resolved must be reported.

4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.

5. Action taken regarding study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. Its outcome: not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, fatal, unknown

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

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

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST 1.1 criteria for solid tumors), 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 (i.e., 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 capmatinib can be found in the [capmatinib Investigator's Brochure]. Information about adverse drug reactions for the other drugs could be found in the respective local labels.

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

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

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant’s general condition

  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, 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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the [ICH-E2D Guidelines]).

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay but under no circumstance later than within 24 hours of obtaining knowledge of the events (Note: if more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and reported on the Serious Adverse Event Report Form in the eCRF (paper forms will only used as backup); all applicable sections of the form must be completed in order to provide a clinically thorough report.

For participants who undergo molecular pre-screening procedures, SAE collection will start upon signing the molecular pre-screening ICF and will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (i.e., 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 (i.e., molecular screen failure), SAE collection ends 30 days after the last study related procedure.

For participants who do not need to undergo molecular pre-screening procedure, SAE collection starts at the time of main study informed consent whether the participant is a screen failure or not and will be reported regardless of relationship to study procedure.

For participants who failed the molecular pre-screening or screening, SAEs will be collected until the time the subject is deemed a molecular screening or screen failure.

For participants treated and/or randomized, SAEs will be collected until 30 days after the participant has discontinued or stopped study treatment.

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

Progression of malignancy (including fatal outcomes) should not be reported as a serious adverse event, except if the investigator considers that the progression is related to study treatment.

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

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

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees (EC) in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 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 the pregnancy consent form. This consent form is necessary to allow the Study Doctor to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up at 1, 3 (for a live birth only) and 12 (for a live birth only) months after the estimated date of delivery to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

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

Pregnancy reporting applies to all study participants for both arms (capmatinib + osimertinib and platinum-pemetrexed arms) as well as for ET.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.2 Steering Committee

A Steering Committee (SC) will be established comprising investigators participating in the trial and/or key opinion leaders in NSCLC (i.e., not being DMC members), and Novartis representatives from the Clinical Trial Team.

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

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

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

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

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP (Good Clinical Practice) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

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

12 Data analysis and statistical methods

The primary efficacy and safety analyses will be performed after observing approximately 162 PFS events as assessed by BIRC.

Data from participating centers in this protocol will be combined, so that an adequate number of participants will be available for analysis. Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, and efficacy, safety and pharmacokinetic measurements. Study data will be analyzed and reported in a primary clinical study report (CSR) based on all participants' data up to the time of the data cut-off date determined for the primary efficacy analysis. Any additional data for participants continuing to receive study treatment past the data cut-off date for the primary CSR, as allowed by the protocol, or continuing in the follow-up parts will be reported at completion of the study in a final CSR. All summaries, listings, figures and analyses will be performed by treatment arms (unless otherwise specified). Screen failure participants, as described in Section 8.1.2, and the reasons for not being randomized will be reported in a listing, but will not be included in any analyses.

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

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

12.1 Analysis sets

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

12.1.1 Full analysis set

For the safety run-in part, the Full Analysis Set (FAS) comprises all participants that received any component of the study drug. According to the intent to treat principle, participants will be analyzed according to the treatment(s) received.

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

12.1.2 Full analysis set brain metastases

The Full Analysis Set – Brain Metastases (FAS-BM) comprises all participants in the FAS who have measurable and/or non-measurable brain metastases at baseline based on randomization strata.

12.1.3 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 actually received, i.e., either capmatinib in combination with osimertinib or platinum-pemetrexed based doublet chemotherapy. The actual treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

12.1.4 Pharmacokinetic analysis set

The Pharmacokinetic Analysis Set (PAS) includes all participants who provided at least one evaluable PK concentration. For a concentration to be evaluable, participants are required to:

- Have received at least one dose of capmatinib + osimertinib
- For steady state trough samples (pre-dose samples) on or after Cycle 2 Day 1 (C2D1), have taken the consistent dose of capmatinib + osimertinib for at least 5 consecutive days prior to sampling except for Cycle 1 Day 1 (C1D1)
- A PK sample is considered as non-evaluable if it is collected after a participant has vomited within 4 hours post-dose.

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

12.1.5 Dose-Determining Set (DDS)

The Dose-Determining Set (DDS) includes all participants from the FAS (safety run in parts) who met the minimum exposure criterion and had sufficient safety evaluations, or experienced a Dose Limiting Toxicity (DLT) during cycle 1 (the first 21 days of dosing).

A participant has met the minimum exposure criterion if the participant takes during the first 21 days of dosing at least 75% of the planned doses for each of the combination drugs (i.e., ≥ 16 out of 21 daily doses for capmatinib and ≥ 16 out of 21 daily doses for osimertinib) and at least 50% of the planned combination doses of the two drugs administered together (i.e., ≥ 11 out 21 daily doses).

Participants who do not experience a DLT during cycle 1 (the first 21 days of dosing) are considered to have sufficient safety evaluations if they have been observed for ≥ 21 days following the first dose, and are considered by both the sponsor and investigators to have enough safety data to conclude that a DLT did not occur. Participants will be analyzed according to the study treatment received as defined for FAS.

12.2 Participant demographics and other baseline characteristics

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

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

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

12.3 Treatments

The Safety Set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented. The exposure related analyses will be presented by dosing regimen for the safety run-in part and by treatment group for the randomized part.

The duration of exposure in weeks to study treatment and for each study drug (capmatinib, osimertinib, and platinum-pemetrexed chemotherapy) as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

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

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

12.4 Analysis supporting primary objectives

The primary objective of randomized phase is to evaluate whether capmatinib in combination with osimertinib prolongs PFS by BIRC according to RECIST 1.1 compared to platinum-pemetrexed based doublet chemotherapy. The analysis will be performed on the FAS.

12.4.1 Definition of primary endpoint(s)

Safety run-in part

The primary endpoint for the safety run-in part is incidence of Dose Limiting Toxicities (DLT) during Cycle 1 of treatment for each dose level associated with administration of capmatinib in combination with osimertinib.

Randomized part

The primary estimand for the randomized phase is defined as in Section 2.1. For the primary estimand, the endpoint PFS is defined as the time from the date of randomization to the date of the first documented disease progression based on BIRC as per RECIST 1.1, or date of death due to any cause, whichever occurs first. In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. PFS will be assessed by BIRC according to RECIST 1.1. Censoring conventions (i.e., handling of missing values, censoring, and discontinuations) are provided in Section 12.4.4.

12.4.2 Statistical model, hypothesis, and method of analysis

Run-in part

The primary endpoint for the safety run-in phase is the incidence of DLT during cycle 1. The dose recommendation decision will be based on the following criteria:

- At least six evaluable participants treated at this dose and regimen.
- No more than two DLT have been observed out of six evaluable participants.
- It is the dose recommended for participants after review of all clinical data by Novartis and Investigators in a dose level review team meeting.

If one of the conditions specified above is not satisfied, dose confirmation cannot be declared and a second cohort may be treated at the lower dose level with capmatinib (400 mg b.i.d.) and osimertinib (40 mg q.d.). The same criteria are applied for this new dose and regimen. If dose confirmation cannot be declared on this lower dose, the randomized part cannot start and the study will end.

DLTs will be listed, and their incidence summarized by primary system organ class, preferred term and worst grade (CTCAE v5.0). Listings and summaries will be based on the DDS.

Randomized part

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

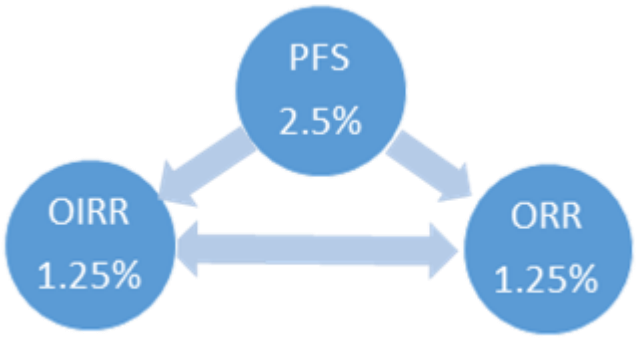
H01: θ1 = 1 vs. HA1: θ1 < 1 where θ1 is the PFS hazard ratio (capmatinib in combination with osimertinib versus platinum-pemetrexed based chemotherapy). The stratification will be based on the stratification factors assigned at randomization (presence of brain metastasis at baseline (presence vs absence) and prior treatment with 3rd generation EGFR TKIs (yes vs no).

The primary efficacy variable, PFS, will be analyzed at the interim analysis and final analysis of a group sequential design (Section 12.7). Analyses will be based on the FAS population according to the randomized treatment group and strata assigned at randomization. The PFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for PFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test. Sensitivity analysis using PFS by investigator assessment will be performed using the same method. Further details will be provided in the SAP.

Multiplicity

In order to conserve the overall type-1 error (one-sided level of significance α=0.025), a graphical gate-keeping approach (Bretz et al 2009, Bretz et al 2011) is used. The primary endpoint of PFS will be tested with α=0.025. If the test is successful, the key secondary endpoints of ORR and OIRR will each be tested with an alpha split following a graphical gate-keeping approach as shown in Figure 12-1. If one of the key secondary endpoint ORR or OIRR is successful, then the 1.25 % alpha assigned to the statistically significant endpoint will be transferred to the other key secondary endpoint and will be tested at a one-sided 2.5% level of significance.

Figure 12-1 Graphical gate-keeping procedure to test the key secondary endpoints in order to control overall type 1 error



12.4.3 Handling of intercurrent events of primary estimand

The intercurrent events for the primary estimands and handling strategies are described in Section 2.1. The handling of the intercurrent events will allow the inclusion of PFS events in the primary analysis prior to inititation of new antineoplastic therapy and is targeting the treatment effect based on the primary endpoint of PFS due to any cause for the combination capmatinib and osimertinib compared to platinum-pemetrexed based doublet chemotherapy for

the target population and any unforeseen intercurrent Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster.

12.4.4 Handling of missing values not related to intercurrent event

Part 1- Run-in part

Participants who are ineligible for the DDS will be excluded from the primary analysis of DLT although their data will be used for all remaining analyses. Other missing data will simply be noted as missing on appropriate tables/listings.

Part 2- Randomized part

Participants whose disease has not progressed or died by the date of the analysis cut-off will have their PFS censored at the time of the last adequate tumor evaluation performed on or before the cut-off date. Clinical deterioration will not be considered as documented disease progression. PFS events will be included in the analysis if it occurs after one missing assessment. PFS will be censored at the last adequate tumor assessment if a participant didn't have an event or the event occurred after two or more consecutive missing tumor assessments.

As per Section 4.6 during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, the number of missing measurements for the primary endpoint PFS may increase and the potential to recover information from intermediate measurements that have been dropped from the visit schedule may decrease. This may affect the power of tests and the precision of estimates for this study. Since it is due to pandemic/epidemic, a reduced visit schedule can be considered to be caused by independent external factors as long as the latter is applied uniformly across the two arms.

12.4.5 Sensitivity analyses

In the randomized part, the following sensitivity analyses for the primary endpoint of PFS will be performed:

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

12.4.6 Supplementary analysis

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

1. an unstratified and covariate unadjusted Cox model.
2. a stratified and covariate adjusted Cox model. A final list of covariates will be defined in the SAP.

Furthermore, a supplementary analysis in the FAS will be performed for PFS by BIRC where PFS will take into account all PFS events regardless of study treatment discontinuation or start of new antineoplastic therapy (treatment policy strategy).

12.4.7 Supportive analyses

As supportive analyses, if the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will also be performed. Important subgroups will be specified in the Statistical Analysis Plan (SAP).

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy endpoint(s)

For the run-in part, the secondary efficacy endpoints are below:

- ORR, DOR, time to response (TTR), and disease control rate (DCR), by investigator assessment per RECIST 1.1.
- PFS by investigator assessment as per RECIST 1.1.

For the randomized part, the key secondary estimands are defined in Section 2.2 for the key secondary endpoints of ORR and OIRR. Other secondary efficacy endpoints are described as the following:

- DOR, time to response (TTR), and disease control rate (DCR), by BIRC as per RECIST 1.1.
- PFS2 (PFS after next-line of treatment) based on local investigator assessment
- Overall Survival
- Duration of intracranial response (DOIR), time to intracranial response (TTIR), and intracranial disease control rate (IDCR) by BIRC as per RANO-BM criteria

[redacted]

12.5.1.1 Key secondary endpoints

Overall response rate (ORR)

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

H01: $\theta 1 - \theta 2 \leq 20$ % vs. HA1: $\theta 1 - \theta 2 > 20$ %, where $\theta 1$, $\theta 2$ are the ORR for the treatment (capmatinib in combination with osimertinib) and control (platinum-pemetrexed based doublet chemotherapy) arms respectively. ORR will be calculated based on the data from the FAS and strata assigned at randomization. The stratification will be based on the stratification factors

assigned at randomization (presence of brain metastasis at baseline (presence vs absence) and previous treatment with 3rd generation EGFR TKIs (yes vs no)).

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

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

Further details will be provided in the SAP.

Overall intracranial response rate (OIRR)

The secondary estimand for OIRR is defined in Section 2.2. OIRR is defined as the proportion of participants with confirmed best overall intracranial response (BOIR) of CR or partial response (PR), and will be assessed by BIRC review. The following null and alternative hypothesis will be tested using stratified Miettinen and Nurminen's method (Miettinen and Nurminen 1985) to address the key secondary efficacy objective for OIRR based on BIRC:

H01: $\theta 1 - \theta 2 \leq 30$ % vs. HA1: $\theta 1 - \theta 2 > 30$ %, where $\theta 1$, $\theta 2$ are the OIRR for the treatment (capmatinib in combination with osimertinib) and control (platinum-pemetrexed based chemotherapy) arms respectively. OIRR will be calculated based on the data from the FAS and strata assigned at randomization. The stratification will be based on the stratification factor assigned at randomization (previous treatment with 3rd generation EGFR TKIs (yes vs no)).

The difference in OIRR and its 95% confidence interval from the stratified Miettinen and Nurminen's method with strata weighting by sample size with a single treatment covariate will be reported.

As a supportive analysis, OIRR per local investigators will be analyzed using the same method as OIRR by BIRC.

Handling of intercurrent events for the key secondary estimands

The intercurrent events for the key secondary estimands and handling strategies are described in Section 2.2. The handling of the intercurrent events will allow the inclusion of all BOR and BOIR in the analysis and is targeting the treatment effect based on ORR and OIRR due to any cause for the combination of capmatinib and osimertinib compared to platinum-pemetrexed based doublet chemotherapy for the target population irrespective of study treatment discontinuation and any Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, the number of missing measurements for the key secondary endpoints (ORR and OIRR) may increase and the potential to recover information from intermediate measurements that have been dropped from the visit schedule may decrease. Since it is due to

pandemic/epidemic, a reduced visit schedule can be considered to be caused by independent external factors as long as the latter is applied uniformly across the two arms.

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

12.5.1.2 Other secondary efficacy endpoints

Duration of response (DOR)

DOR by BIRC is a secondary endpoint. DOR only applies to participants whose BOR is CR or PR according to RECIST 1.1 based on tumor response data. DOR is defined as the time from the date of first documented response (CR or PR) to the first documented progression per RECIST 1.1 or death due to any cause. If a participant has not had an event, DOR is censored at the date of last adequate tumor assessment. Participants who never achieved a BOR of CR or PR will be excluded from the analysis. The distribution function of DOR will be estimated using the Kaplan-Meier method. Definition of last adequate tumor assessment is provided in Section 16.1. DOR will be analyzed based on the data from the FAS. Median DOR, with corresponding 95% CI, and 25^{th} and 75^{th} percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. DOR will be also assessed by local review and will be analyzed with the same method as supportive analysis.

Kaplan-Meier (KM) estimates for DOR proportions (by BIRC and by investigator) at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

Time to response (TTR)

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

Participants without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e., LPLV−FPFV) for participants with a PFS event, or at the date of the last adequate tumor assessment for participants without a PFS event. TTR will be summarized using the Kaplan-Meier (KM) method, based on data from the FAS. Median TTR, with corresponding 95% CI, and 25^{th} and 75^{th} percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for TTR proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

Disease control rate (DCR)

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

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

Progression-free survival 2 (PFS2)

PFS2 is defined as time from date of randomization to the first documented progression on the next line therapy or death from any cause, whichever occurs first. The PFS2 distribution will be estimated using the Kaplan-Meier method for each treatment arm. The hazard ratio for PFS2 will be calculated, along with its 95% confidence interval, using a Cox model stratified by randomization stratification factors. PFS2 analysis will be performed using data from FAS.

Overall survival (OS)

OS is defined as the time from the date of randomization to the date of death due to any cause.

If a participant is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cut-off date. OS will be summarized using the KM method, based on data from the FAS.

Median OS with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented.

The hazard ratio for OS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for PFS analysis.

The analysis of OS will be performed at the time of the analysis for the primary endpoint of PFS.

Final analysis of OS will be performed at the end of the study as defined in Section 9.2.

There is no hypothesis testing for OS and thus it is not included in the group sequential testing procedure.

Sensitivity analyses for OS may be performed and further details will be provided in the SAP.

Duration of intracranial response (DOIR)

DOIR only applies to participants whose confirmed BOIR is CR or PR per RANO-BM criteria as assessed by BIRC review. DOIR is defined as the time from the date of first documented intracranial response of either CR or PR to the date of the first documented intracranial progression per RANO-BM criteria as assessed by BIRC review or the date of death due to any cause. Participants with a confirmed intracranial CR or PR will be censored if they have disease progression in organs other than brain and have no scans in brain after that. Participants will also be censored if they did not have an event. The censoring date will be the date of the last adequate tumor assessment in brain. DOIR will be summarized using the KM method. Median DOIR, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for DOIR proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

Time to intracranial response (TTIR)

TTIR is defined as the time from the date of randomization to the date of the first documented intracranial response of either CR or PR per RANO-BM criteria as assessed by the BIRC review, which must be subsequently confirmed (date of initial response is used, not date of confirmation). All participants in the FAS-BM will be included in TTIR calculations.

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

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

Intracranial disease control rate (IDCR)

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

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

12.5.2 Safety endpoints

For the safety run-in part, summary tables and listings will be presented by dose regimen using the safety set. For the randomized part, all listings and tables will be presented by treatment group. For all safety analyses, the safety set will be used.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs). Further details will be included in the SAP.

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

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication,
2. On-treatment period: from date of first administration of study treatment to the earlier of
   - 30 days after date of last administration of study treatment (including start and stop date),
   - the date prior to start of extension treatment with capmatinib + osimertinib following crossover from control arm,

3. Post-treatment period: starting at day 30+1 after last dose of study medication or first day of extension treatment with capmatinib + osimertinib.

Further details of the analysis and data reporting from participants who crossover from platinum-pemetrexed based doublet chemotherapy arm to capmatinib in combination with osimertinib therapy will be provided in the SAP.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

by treatment, primary system organ class and preferred term.

by treatment, primary system organ class, preferred term and maximum severity.

by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

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

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

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

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

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

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

All AEs, deaths, and serious adverse events (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Vital signs

All vital signs data will be summarized by treatment and visit/time.

12-lead ECG

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

2. Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented.

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

Clinical laboratory evaluations

All laboratory data will be summarized by treatment group and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

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

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

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low/normal/high (based on laboratory normal ranges).

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

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

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

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 5.0 grades to compare baseline to the worst on-treatment value.

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

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

[redacted]

12.5.3 Pharmacokinetics

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

Capmatinib, osimertinib, AZ5104 and AZ7550 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided pre-dose (trough) concentrations by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (coefficient of variation) (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ (< 1.0 ng/mL) will be treated as zero in summary statistics and for PK parameter calculations.

For C1D1 and C2D1 in run-in part (intensive PK), pharmacokinetic parameters (i.e., AUC, C_{min}, C_{max}, T_{max}, T1/2) will be calculated by noncompartmental methods and listed by subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is *Tmax* where median, minimum, and maximum will be presented.

PK-QTc Analysis will be performed to evaluate the relationship between osimeritinib concentration and change from baseline in QT corrected for heart rate and the details will be provided in the SAP.

12.5.4 Patient reported outcomes

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

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

The distribution of time to symptom deterioration will be analyzed by treatment group for patient scores from the EORTC QLQ-C30, QLQ-LC13 and NCCN FBrSI questionnaires. It will be estimated using the Kaplan-Meier method and the median time along with two-sided 95% CIs will be presented. The hazard ratio will be estimated, along with its 95% confidence interval, using a stratified Cox proportional hazard model using the randomization stratification factor. Further details will be specified in the SAP.

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

[redacted]

12.7 Interim analyses

Run-in part

No formal interim analysis is planned. The decision on the recommended dose of capmatinib in combination with osimertinib in the run-in part will be based on analyses performed after at least 6 evaluable participants completed the first cycle. Dose recommendation decisions will be made by Investigators and Novartis study personnel 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 ≥ 2 toxicity data during Cycle 1 and PK data from evaluable participants. Details of this procedure and the process for communication with investigators are provided in Section 6.5.1.2.

Randomized part

One interim analysis is planned after approximately 65 of the 162 targeted PFS events (i.e., at approximately 40% information fraction) have been documented (expected around 18.5 months from the date of first participant randomized in the study). The primary intent of the interim analysis is to stop early for futility. Approximately 130 (57.8%) participants are expected to be randomized at the time of the interim analysis, i.e., when approximately 65 PFS events have occurred. To be conservative, it is assumed that both futility and efficacy analyses are performed at the interim analysis. However, there is no plan to stop the study for efficacy at the interim analysis. An α-spending according to Haybittle-Peto stopping boundary with fixed p-value=0.0001 will be used for the IA for efficacy.

A gamma spending function ($\gamma = 1$) will be used as a beta-spending function to determine the non-binding futility boundary.

Based on the choice of alpha-spending function described above and if the interim analysis is performed exactly at 65 PFS events, the futility boundary in terms of the Z statistic scale at the interim is calculated as Z=-0.472. The observed z-statistic has to be greater than Z = -0.472 to conclude futility.

Since the observed number of events at the interim analysis may not be exactly equal to the planned 65 PFS events, the futility boundaries will need to be re-calculated using the pre-specified α-spending and β-spending functions and based on the actual number of observed events at interim and the total number of targeted events to calculate the exact information

fraction. The observed hazard ratio at the interim analysis will then be compared against the re-calculated or futility boundary.

If the study continues to the final PFS analysis, the final PFS analysis will be performed when approximately 162 PFS events have been documented. If exactly 65 events are observed at the interim analysis, the study continues and exactly 162 events are obtained at the final analysis, the observed p-value will have to be less than 0.025 to declare statistical significance. In practice, the final analysis will be based on the actual number of PFS events documented at the cut-off date for the final PFS analysis and the alpha already spent at the interim analysis. The boundary for the final analysis will be derived accordingly from the pre-specified α-spending such that the overall significance level across all analyses is maintained at 0.025.

The statistical properties of the group sequential design are summarized in Table 12-1 below.

Table 12-1 Simulated probabilities to stop for futility at the interim or final PFS analysis

Scenario	Look	# PFS events	Simulated cumulative probabilities (%)	
			Stop for efficacy	Stop for futility
Under H0 (HR=1)	Interim	65	0.02	67.61
	Final	162	2.79	97.21
Under Ha (HR=0.529)	Interim	65	13.60	2.23
	Final	162	95.63	4.37
Under other Ha (HR=0.7)	Interim	65	1.38	18.42
	Final	162	54.84	45.16

NOTE: Simulation is performed in East (6.4) with number of simulations = 10,000 and randomization seed =100

To be conservative, a small alpha-will be spent based on Haybittle-Peto boundary with fixed p-value=0.0001 (as implemented in East 6.4) for the key secondary endpoints of ORR and OIRR. However, there is no intention to stop the study for efficacy at interim analysis. Approximately 57.8% participants are expected to be randomized at the time of the interim analysis. If the primary endpoint of PFS meets the futility stopping criteria, the study will be discontinued and no further tests on the key secondary endpoints will be performed. In addition, OS will be summarized for hazard ratio at the time of the final PFS analysis.

The interim analyses will be performed by an independent statistician (not involved with the conduct of the study). Further details will be described in the DMC charter. The results of the interim analyses will be provided to the DMC by the independent statistician.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Run-in part

No formal statistical power calculations to determine sample size were performed for this part of the study. Approximately 10 participants will be enrolled with the starting dose of capmatinib (400 mg b.i.d.) and osimertinib (80 mg q.d.) to have at least 6 evaluable participants. If the

initial dose is not considered safe and tolerable, additional 10 more participants could be enrolled at a lower dose level (DL-1) of capmatinib (400 mg b.i.d.) and osimertinib (40 mg q.d.) to achieve additional 6 evaluable participants.

Randomized part

The sample size calculation is based on the primary variable PFS. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2

Based on available data Mok et al (2017) and the negative prognostic impact of the MET dysregulation and T790M negative population, the median PFS in the control arm (platinum - pemetrexed based doublet chemotherapy) is expected to be around 4.5 months. It is expected that treatment with capmatinib in combination with osimertinib (experimental treatment arm) will result in 47.1% reduction in the risk of progression and/or death, i.e., an expected overall hazard ratio of 0.529 (which corresponds to an increase in median PFS to 8.5 months under the exponential model assumption).

Then in order to ensure at least 95% power to test the null hypothesis: PFS hazard ratio = 1, versus the specific alternative hypothesis: PFS hazard ratio = 0.529, it is calculated that a total of 162 PFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 2:1 ratio, and a 2-look group sequential design with a gamma spending function (γ=1) using information fractions of 40% to define a non-binding futility rule at the interim analysis.

Assuming that enrollment will continue for 32 months at a uniform rate of 7 participants per month, a total of 225 participants will need to be randomized to observe the targeted 162 PFS events at about 5 months after the randomization date of the last participant, i.e., 37 months after the randomization date of the first participant. Then assuming losses to follow-up for PFS of 20%, the required sample size of the study is 225 randomized participants, which requires an accrual rate of 7 participants per month during the 32-month recruitment period. The sample size of 225 participants will be randomly assigned to each treatment arm in a 2:1 ratio (150 participants in the experimental treatment arm, 75 participants in the control arm). These calculations were made using the software package East (6.4).

12.8.2 Secondary endpoint(s)

Overall Response Rate (ORR)

ORR, as the key secondary variable, will be formally statistically tested, provided that the primary variable PFS is statistically significant. The hypotheses to be tested and details of the testing strategy are provided in Section 12.5.1. Based on available data (Soria et al 2015, Mok et al 2017), the ORR in the control arm is expected to be around 35%. It is hypothesized that treatment with capmatinib and osimertinib will result in a 20% increase in the ORR for treatment, i.e., an expected ORR of 55%. The ORR will be tested at the time of the final PFS analysis. Based on the number of participants that are planned to be enrolled in this study to provide sufficient power for the primary endpoint (225 participants), and randomization ratio of 2:1; the test for ORR (H01: $\theta 1 - \theta 2 \leq 20$ % vs. HA1: $\theta 1 - \theta 2 > 20$ %) based on difference in ORR without the stratification factors with pooled estimate of variance will have 72.8% power

with a one-sided alpha of 0.0125 if OIRR is not significant or 81.6% power at 2.5% level of significance if OIRR is significant.

The approximate treatment difference required to reach the bound (Δ ORR) is 15.8% when OIRR is not significant and 13.9% when OIRR is significant.

Overall Intracranial Response Rate (OIRR)

OIRR, as the key secondary variable, will be formally statistically tested, provided that the primary variable PFS is statistically significant. The hypotheses to be tested and details of the testing strategy are provided in Section 12.5.1. Based on available data (Schuler et al 2016), the OIRR in the control arm is expected to be around 25%. It is hypothesized that treatment with capmatinib and osimertinib will result in a 30% increase in the OIRR for treatment, i.e., an expected OIRR of 55%. The OIRR will be tested at the time of the final PFS analysis. Based on the number of participants that are planned to be enrolled in this study (225 participants) and approximately 30% of participants will have brain metastasis at randomization, it is expected that there will be approximately 68 participants available in the brain metastasis analysis set. The test for OIRR (H01: $\theta 1 - \theta 2 \leq 30$ % vs. HA1: $\theta 1 - \theta 2 > 30$ %) based on difference in OIRR without the stratification factor with pooled estimate of variance will have 54.5% power with a one-sided alpha of 0.0125 if ORR is not significant or 66.3% power at 2.5% level of significance if ORR is significant.

The approximate treatment difference required to reach the bound (Δ OIRR) is 28.7% when ORR is not significant and 25.1% when ORR is significant.

Overall Survival (OS)

At the time of the final analysis of PFS, the hazard ratio of OS will be estimated. A positive trend of OS hazard ratio in favor of the treatment arm (hazard ratio <1) is expected to support the efficacy conclusion from PFS. Since OS is not powered given the limitation of sample size and enrollment, no test will be conducted for OS.

The number of OS events expected to observe an OS hazard ratio less than 1 are summaried in the Table 12-2:

Table 12-2 Number of OS events expected at the time of the final PFS analysis under different assumptions and scenarios

Scenario	Median OS (months) in Control Arm	Median OS (months) in Treatment Arm	# OS events
HR = 0.70	14	20	112
HR = 0.75	14	18.67	114
HR = 0.85	14	16.47	117

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

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

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

The protocol, protocol amendments, ICF, IB, and other relevant documents must be submitted to Health Authorities and IRB/IEC by the investigator and reviewed and approved by the HA and the IRB/IEC before the study is initiated.

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., [Clinicaltrials.gov], EudraCT etc.). For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

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

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

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

13.5 Participant Engagement

Participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis. Examples of Patient Engagement initiatives that might be included in this study are:

- Thank You letter
- Plain language trial summary – after CSR publication
- Individual study results – after CSR publication
- Trial Feedback Questionnaires (TFQ) – end of trial

14 Protocol adherence

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

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

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

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16.1.1 Introduction

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

The efficacy assessments described in Section 16.1.2 and the definition of best response in Section 16.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.1.3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 16.1.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009).

16.1.2.1 Definitions

16.1.2.1.1 Disease measurability

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

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

For patients without measurable disease see Section 16.1.3.2.8.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10 mm whichever is greater - e.g., the minimum non-nodal lesion size for CT/MRI with 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.

16.1.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g., in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients are excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.1.3.2.8.

16.1.2.2 Methods of tumor measurements - 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.

16.1.2.3 Baseline documentation of target and non-target lesions

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

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

clinically). Each target lesion must be uniquely and sequentially numbered on the eCRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g., clinical examination, photography) should be at least 10 mm in longest diameter. See Section 16.1.2.1.1.
- **Nodal target:** See Section 16.1.2.1.1.

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

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

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 16-1) and non-target lesions (Table 16-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-3) as well as the presence or absence of new lesions.

16.1.2.4.1 Follow-up and recording of lesions

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

Non-nodal lesions

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

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

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

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

Nodal lesions

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

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

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

16.1.2.4.2 Determination of target lesion response

Table 16-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR)	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR)	At least 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 emasured 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 and increase in lesions which would qualify for PD
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline [3]

[1.] SOD for CR may not be zero when nodal lesions are part of target lesions
[2.] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3.] In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgement based on the available information (see Notes on target lesion response and methodology change in Section 16.1.2.2)

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as 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 eCRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of
- 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 lesions decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.

- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g., a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.1.2.4.3 Determination of non-target lesion response

Table 16-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions [1]
Non-CR/Non-PD	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using different method than baseline [2]
[1.] The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail [2.] It is recommended that the investigator and/or central reviewer should use expert judgement to assign a Non-UNK response whenever possible (see notes section for more details)	

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned
- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e., < 10 mm). If any of the non-target lesions are still present, or there are

any abnormal nodal lesions (i.e., ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK)

- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 16.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.1.2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 16.1.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short exis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase. **FDG-PET:** can complement CT scans in assessing progression (particularly possible for "new" disease). See Section 16.1.2.2.

16.1.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 16-3.

Table 16-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK

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

[1.] This overall lesion response also applies when there are no non-target lesions identified at baseline
[2.] Once confirmed PR was achieved, all these assessments are considered PR
[3.] As defined in Section 16.1.2.4

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

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

16.1.3 Efficacy definitions

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

16.1.3.1 Best overall response

The best overall response 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 weeks 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 (Dent et al 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).

16.1.3.2 Time to event variables

16.1.3.2.1 Progression-free survival

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

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

16.1.3.2.2 Overall survival

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

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

16.1.3.2.3 PFS2

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

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

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

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

16.1.3.2.4 Time to treatment failure

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

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

16.1.3.2.5 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.

16.1.3.2.6 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 16.1.3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options:

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

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

16.1.3.2.7 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 16.1.3.2.7).

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

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

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

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

consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 16-4.

Table 16-4 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/Non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD
[1] As defined in Section 16.1.2.4		

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for 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.

16.1.3.2.9 Sensitivity analyses

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

Based on definitions outlined in Section 16.1.3.2.7, and using the draft FDA guideline on endpoints (FDA 2018) as a reference, the following analyses can be considered:

Table 16-5 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	Cendored
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 the situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anticancer therapy (4) Date of secondary anticancer 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)

Situation	Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
[1.] Definitions can be found in Section 16.1.3.2.7 [2.] After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.1.3.2.7 [3.] The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death		

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

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

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

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

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

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e., progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

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

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

The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

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

Additional suggestions for sensitivity analyses

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

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

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

16.1.4 Data handling and programming rules

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

16.1.4.1 Study/project specific decisions

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

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

16.1.4.2 End of treatment phase completion

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

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

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

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

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

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

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

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

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.1.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e., any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e., if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the

quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

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

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

16.1.4.5 Programming rules

The following should be used for programming of efficacy results:

16.1.4.5.1 Calculation of time to event variables

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

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

16.1.4.5.2 Incomplete assessment dates

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

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 16.1.3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

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

16.1.4.5.3 Incomplete dates for last known date patient alive or death

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

16.1.4.5.4 Non-target lesion response

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

16.1.4.5.5 Study/project specific programming

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

16.1.4.5.6 Censoring reason

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

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore 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 16-5)
- 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 16.1.3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

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

16.2 Appendix 2: Response assessment in neuro-oncology (RANO) criteria for Brain Metastases

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16.2.1 Introduction

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

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

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

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

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

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

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

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

16.2.2 Efficacy assessments

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

16.2.2.1 Definitions

16.2.2.1.1 Disease measurability

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

Measurable disease

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

Non-measurable disease

Non-measurable disease includes all other lesions, including:

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

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

16.2.2.1.2 Eligibility based on measurable disease

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

16.2.2.2 Methods of tumor measurement general guidelines

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

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

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

16.2.2.2.1 Special circumstances

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

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

- If the subsequent assessment shows that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

16.2.2.3 Baseline documentation of target and non-target lesions

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

Target lesions

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

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

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

Non-Target lesions

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

Documentation of previously treated lesions

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

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 16-6) and non-target lesions (Table 16-7) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-8) as well as the presence or absence of new lesions,

corticosteroid usage relative to baseline, ECOG performance scale and other clinical evaluation findings relative to baseline.

16.2.2.4.1 Follow-up and recording lesions

At each visit and for each lesion the actual date of the MRI which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit, all of the separate lesion evaluation data are examined by the investigator/local reader in order to derive the overall visit response.

16.2.2.4.2 Determination of response/progression

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

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

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

Determination of target lesion response

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

Table 16-6 Response assessment of target lesions

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

Determination of non-target lesion response

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

Table 16-7 Response assessment of non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete response (CR)	Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions
Non-complete response or non-progressive disease (Non-CR/Non-PD)	Persistence of one or more non-target CNS lesion or lesions
Progressive disease (PD)	Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease
Not evaluable	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different technique than baseline

New lesions

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

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

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

Corticosteroids

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

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

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

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

Clinical Status

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

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

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

16.2.2.4.3 Evaluation of overall lesion response

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

Table 16-8 Overall Lesion Response at each assessment

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
Target Lesions	None	≥ 30% decrease in sum LD relative to baseline	< 30% decrease relative to baseline but < 20% increase in sum LD relative to nadir [1]	≥ 20% increase in sum LD relative to nadir [1]
Non-target Lesions [2]	None	Stable or improved	Stable or improved	Unequivocal PD [3]
New Lesion(s)[4]	None	None	None	Present [3]
Corticosteroids compared to baseline	None	Stable or decreased	Stable or decreased	Not applicable [5]
Clinical Status compared to baseline	Stable or improved	Stable or improved	Stable or improved	Worse [3]

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
Requirement for Response	**All**	**All**	**All**	**Any [5]**

[1.] Nadir: the smallest sum of diameter of all target lesions recorded at or after baseline
[2.] Non-target lesions response: stable (Non-CR/Non-PD), improved (CR)
[3.] Progression occurs when this criterion is met
[4.] A new lesion is one that was not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone do not define progression
[5.] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration (see Section 16.2.2.4.2).
Sum LD: sum of longest diameters
Not evaluable (NE) overall lesion response is described in Section 16.2.2.4.3
Corticosteroids and clinical status based on investigators' opinion (see Section 16.2.2.4.2)

Complete response (CR)

All of the following criteria must be met:

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

Partial response (PR)

All of the following criteria must be met:

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

Stable disease (SD)

All of the following criteria must be met:

1. Less than 30% decrease from baseline but less than 20% increase from nadir in the sum of longest diameters of all target lesions
2. Does not qualify for CR, PR, or PD
3. No new lesions

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

Progressive disease (PD)

Any of the following criteria must be met:

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

Not evaluable status (NE)

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

16.2.2.4.4 CNS and non-CNS Response Assessment

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

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

Table 16-9 CNS and non-CNS response assessment

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

16.2.3 Efficacy definitions

16.2.3.1 Best overall intracranial response

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

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

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

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required

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

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

16.2.3.2 Endpoints

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

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

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

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

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

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

16.2.3.3 Definitions of dates

Assessment dates

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

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

Start dates

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

- Date of first documented response is the assessment date of the first overall lesion response of CR / PR when this status is later confirmed. The date of initial response is used, not date of confirmation.

End dates

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

- Date of death due to any cause is the date of death due to "Study indication" or "Other"
- Date of intracranial progression is the first assessment date at which the overall lesion response was recorded as progressive disease in the brain
- Date of last adequate intracranial tumor assessment is the date the last tumor assessment in brain with overall lesion response of CR, PR or SD was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments in brain are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.

Secondary anti-cancer therapy date

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

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

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

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

It is recommended that any participants with only non-measurable disease at baseline should be included in the main analysis (Intent-To-Treat approach) of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients with only non-measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 16-10.

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

Criteria	Complete Response	Non-CR/Non-PD	Progressive Disease
Non-target Lesions [1]	None	Stable or improved	Unequivocal PD [2]
New Lesions [3]	None	None	Present [2]
Corticosteroids compared to baseline	None	Stable or decreased	Not applicable [4]
Clinical Status compared to baseline	Stable or improved	Stable or improved	Worse [2]
Requirement for Response	**All**	**All**	**Any [4]**

[1.] Non-target lesions response: stable (Non-CR/Non-PD), improved (CR)
[2.] Progression occurs when this criterion is met
[3.] A new lesion is one that is not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone do not define progression
[4.] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration (see Section 16.2.2.4.2)
Not evaluable (NE) overall lesion response is described in Section 16.2.2.4.3
Corticosteroids and clinical status based on the investigators' opinion (see Section 16.2.2.4.2)

16.2.3.4.1 Evaluation of overall lesion response

Complete response (CR)

All of the following criteria must be met:

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

Non-CR/Non-PD

All of the following criteria must be met:

1. Does not qualify for CR or PD
2. No new lesions
3. The corticosteroid dose at the time of the scan evaluation is not greater than the corticosteroid dose at the time of the baseline MRI scan

4. Stable or improved clinical status per investigator supported ECOG performance status scale compared to baseline.

Progressive disease (PD)

Any of the following criteria must be met:

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

16.2.3.4.2 Best overall intracranial response

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

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

16.3 Appendix 3: Permitted concomitant therapy requiring caution and/or action

Table 16-11 Drugs to be used with caution during co-administration with capmatinib and osimertinib

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, 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
CYP1A2 substrate with NTI	theophylline, tizanidine
P-gp substrates [1]	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, atorvastatin, boceprevir, bosentan, carvedilol, caspofungin, ceritinib, colchicine, cyclosporine, dabigatran, digoxin, docetaxel, doxepin, doxorubicin, eribulin, everolimus, fentanyl, fexofenadine, fidaxomicin, fluvastatin, fosamprenavir, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, linagliptin, linezolid, loperamide, losartan, maraviroc, mirabegron, nadolol, naloxegol, nateglinide, nevirapine, nintedanib, olodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, proguanil, ranolazine, riociguat, risperidone, ritonavir, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
BCRP substrates [1]	atorvastatin daunorubicin, dolutegravir, doxorubicin, ethinyl estradiol, hematoporphyrin, imatinib, irinotecan, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitor	Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
H_2-receptor antagonists	cimetidine, famotidine, nizatidine, ranitidine
Antacids	aluminum carbonate, aluminum hydroxide, calcium carbonate, calcium hydroxide, bismuth subsalicylate

Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (drug-interactions.medicine.iu.edu/Main-Table.aspx), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies".

This list may not be exhaustive and could be updated periodically. Please refer to the above mentioned source of 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.

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

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

16.4 Appendix 4: Prohibited QT prolongation concomitant medication for capmatinib and osimertinib

Drugs with a known risk of Torsades de Pointes (TdP) are prohibited. For identification of drugs with known risk of TdP please refer to qtdrugs.org (refer to Table 16-12).

Table 16-12 Drugs with a known risk of Torsades de Pointes

Torsades de Pointes Risk	Generic Name
Known	Aclarubicine, amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, cesium chloride, chloroquine, chlorpromazine, chlorprothixene, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, grepafloxacin, halofantrine, haloperidol, hydroquinidine, hydroxychloroquine, ibogaine, ibutilide, levofloxacin, levomepromazine, levomethadyl acetate, levosulpiride, mesoridazine, methadone, moxifloxacin, nifekalant, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terfenadine, terlipressin, terodiline, thioridazine, vandetanib
Check crediblemeds.org/healthcare-providers/drug-list for the most updated list. This may not be an exhaustive list, will be updated periodically. Note: if a medication is listed in more than one table, the more stringent practice is to be applied	

16.5 Appendix 5: Prohibited drugs

Table 16-13 Capmatinib and osimertinib: prohibited drugs

Mechanism of Interaction	**Drug Name**
Strong CYP3A inducer	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (*Hypericum perforatum*)
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 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 source of information.	