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INC280 (capmatinib)

Clinical Trial Protocol CINC280AUS12 / NCT04926831

Phase II trial of neoadjuvant and adjuvant capmatinib in participants with stages IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) NSCLC with MET exon 14 skipping mutation or high MET amplification – Geometry-N

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List of abbreviations

AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCRP	Breast Cancer Resistance Protein
b.i.d.	bis in die/twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CLIA	Clinical Laboratory Improvement Amendments
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
CO_2	Carbon Dioxide
CQA	Clinical Quality Assurance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computerized Tomography
CTC	Common Terminology Criteria
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DIN	Drug Inducted Nephrotoxicity
DQF	Data Query Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
ERCP	Endoscopic Retrograde Cholangiopancreatography
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FDA	Food and Drug Administration
FEV	Forced Expiratory Volume
FISH	Fluorescence in situ hybridization
FSH	Follicle Stimulating Hormone
GCN	Gene Copy Number
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl Transferase
h	Hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus

HCV	Hepatitis C Virus
hCG	Human Chorionic Gonadotropin
HED	Human Equivalent Dose
HEOR	Health Economics & Outcomes Research
HIV	Human immunodeficiency virus
HGF	Human Growth Factor
i.v.	intravenous
[redacted]	
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
LDH	lactate dehydrogenase
LFT	Liver Function Test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
MET	Mesenchymal Epithelial Transition
METex14	MET exon 14 skipping
mg	milligram(s)
mL	milliliter(s)
MPR	Major Pathologic Response
MRI	Magnetic Resonance Imaging
Nab	Neutralizing antibody
NCI	National Cancer Institute
NGS	Next Generation Sequencing
p.o.	oral(ly)
PA	posteroanterior
PC	Personal Computer
PD	Pharmacodynamic(s)
PET	Positron Emission Tomography
PFT	Pulmonary Function Test(s)
PK	Pharmacokinetic(s)
PS	Performance Status
PT	Prothrombin Time
QD	Once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula

R Value	ALT/ALP x ULN
RAP	The Report and Analysis Plan
RBC	Red Blood Cell(s)
RDC	Remote Data Capture
RECIST	Response Evaluation Criteria In Solid Tumors
RoW	Rest of World
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sCR	serum creatinine
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SoC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TKI	Tyrosine Kinase Inhibitor
TBL	Total Bilirubin Level
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
WBC	White Blood Cell(s)
WHO	World Health Organization
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 specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (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)
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the 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
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	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
Sequence number	A unique medication number on the label of each bottle of medication
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)

Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
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.
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
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
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.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Enrollment number	A unique identifier assigned to each enrolled participant
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 treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.

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.
Victim drug	The drug that is affected by the drug-drug interaction
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 1 (17-Mar-2023)

Amendment rationale

[redacted]

Additionally, this amendment clarifies the definition of the secondary endpoint, overall response rate (ORR); overall response rate will be based on the best overall response (BOR) by the RECIST 1.1 analysis performed prior to surgery. Since BOR is being determined at the assessment prior to surgery, a confirmatory assessment, 4 weeks later, will not be required, because it is not feasible to delay patient surgery for that reason.

This amendment also includes information that participants should not be receiving live vaccines during treatment or radiotherapy while on study.

The study is currently open at 9 participating sites and 4 patients have been enrolled. This amendment will have no impact on patient safety.

Additional minor protocol language clarifications and updates are made throughout the amendment.

Changes to the protocol

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

- Section 2.1: Updated the variable to clarify evaluable participants.
- Section 3: updated the number of participants with MPR needed to expand a cohort from 1 to 2. [redacted]
- Figure 3-1: Added a footnote indicating adjuvant chemotherapy is optional and at the discretion of the treating physician [redacted].
- Section 4.5.1: Updated to include most recent safety information
- Section 6.2.1: Clarified that radiotherapy should not be given to participants.
- Section 6.2.2: Added statement that live vaccines should not be administered while participant is on treatment and for 30 days after last dose of treatment.
- Section 6.7.1: Clarified that all unused study treatment should be destroyed at site, when permitted by local regulations and site is able to destroy compliantly.

[redacted]

- Section 8.4.5: Added language defining women of childbearing potential.

[redacted]

- Section 9.1.1: Added language to clarify EOT and safety follow up.

- Section 9.2: Clarified study completion definition.

[redacted]

- Section 12.4.3: Removed intercurrent events for primary estimand and added intercurrent events for the supplementary estimand.
- Section 12.4.4: clarified that for the primary estimand, only participants with non-missing MPR will be considered for the MPR evaluation and for the supplementary estimands, patients with missing MPR values will be considered non-responders.
- Section 12.5.1: Clarified that best overall response will be determined at the assessments performed prior to surgery. Due to timepoint of assessment, and need for patients to proceed to surgery, there will not be a confirmatory response assessment 4 weeks later.
- Section 12.5.2: Clarified safety follow up is 30 days

[redacted]

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

IRBs/IECs

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

The changes described in this amended protocol 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

	CINC280AUS12
Full Title	Phase II trial of neoadjuvant and adjuvant capmatinib in participants with stages IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) NSCLC with MET exon 14 skipping mutation or high MET amplification
Short Title	Geometry-N
Sponsor and Clinical Phase	Novartis
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine if neoadjuvant capmatinib followed by surgical resection and adjuvant treatment with capmatinib can improve outcomes in participants with IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) lung cancers with *MET* exon 14 mutations and/or high MET amplification beyond those achieved with surgery, chemotherapy, and radiation. Capmatinib is an effective MET kinase inhibitor. Coupled with its tolerability, it is an ideal drug to use in the preoperative setting. It has no effects on wound healing and venous thromboembolism. Myelosuppression of any degree is uncommon with capmatinib.
Primary Objective(s)	To determine the major pathologic response (MPR) in resection specimens following neoadjuvant capmatinib in 2 cohorts. Cohort A: MET exon 14 skipping mutation, irrespective of MET gene copy number (GCN); Cohort B: High MET amplification (MET: GCN ≥10)
Secondary Objectives	• To determine the complete pathologic response following neoadjuvant capmatinib therapy in each cohort • To evaluate safety and tolerability of capmatinib • To assess disease free survival with adjuvant therapy with capmatinib • To assess overall response rate post neoadjuvant treatment with capmatinib in each cohort
Study design	This is a phase II, two cohort, two stage, study of capmatinib given for 8 weeks prior to surgical resection, followed by three year capmatinib treatment in adjuvant setting and a two year survival follow-up. There will be 2 molecularly defined cohorts enrolling in parallel: Cohort A: MET exon 14 skipping mutations, irrespective of MET GCN or Cohort B: high level MET amplification (MET: GCN ≥ 10). [redacted]
Study population	Newly diagnosed participants with clinical stages IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) lung cancers with MET exon 14 mutations and/or high level MET amplification (MET: GCN ≥ 10).
Key Inclusion criteria	1. Histologically confirmed NSCLC stage IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) (per AJCC 8th edition), deemed suitable for primary resection by treating surgeon (T4 tumors with mediastinal organ invasion are not eligible for enrollment).

	2. Participants must be eligible for surgery and scheduled for surgical resection within approximately 2 weeks after the last does of neoadjuvant study treatment. 3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
Key Exclusion criteria	1. Participants with unresectable or metastatic disease. All participants should have brain imaging (either Magnetic Resonance Imaging (MRI) brain or Computed Tomography (CT) brain with contrast) prior to enrollment to exclude brain metastasis. 2. Presence or history of a malignant disease that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type. 3. Prior treatment with any MET inhibitor or HGF-targeting therapy. 4. Participants with other known oncogenic driver alterations. 5. Prior systemic anti-cancer therapy (chemotherapy, immunotherapy, biologic therapy, vaccine) or investigational agents for NSCLC. 6. Participants with known hypersensitivity to capmatinib and any of the excipients of capmatinib (crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes).
Study treatment	Capmatinib (INC280)
Treatment of interest	Capmatinib in the neoadjuvant and adjuvant setting
Efficacy assessments	**MPR:** Response will be assessed locally at the time of surgery (by number of subjects with ≤ 10% residual viable cancer cells). **Radiology tumor assessments:** Neoadjuvant: By investigator at screening and once before surgery. Response by RECIST 1.1. Adjuvant: Following surgery, imaging assessments will be done at the initiation of adjuvant therapy and then every 12 weeks (± 7 days) for the first year of adjuvant treatment and then every 26 weeks during years two and three of treatment.
Key safety assessments	• Physical examination • ECOG PS • Body weight and vital signs • Laboratory assessments, including hematology, chemistry, and urinalysis • Pregnancy tests for women of child-bearing potential (serum pregnancy test at screening for all female participants) • Adverse events (AEs) the severity, the relationship with to study treatment and the seriousness
[redacted]	[redacted]

Data analysis	Primary efficacy analysis will be performed using Full Analysis Set. Primary efficacy variable is the MPR rate. [redacted] An interim analysis will be performed for both the cohorts individually after Stage 1 of the study to make a determination to go or not to the Stage 2 based the pre-specified efficacy threshold. Efficacy and safety data will be summarized. All secondary [redacted] will be summarized descriptively. Categorical data will be presented in frequencies and percentages. For continuous data descriptive statistics (mean, standard deviation, median 25th and 75th percentiles, min and max) will be provided. As appropriate 95% confidence interval will be reported. Kaplan Meier's estimates will also be reported for the time to event variables. All summarized safety data will also be presented. A final analysis will be performed when all participants complete the treatment period or discontinue earlier. As appropriate, annual interim analyses of the data may be performed for publication purposes. [redacted]
Key words	Non-small cell lung cancer (NSCLC), MET pathway, MET exon 14 skipping mutation (METex14), MPR (Major Pathological Response)

1 Introduction

1.1 Background

An estimated 2.2 million people were diagnosed globally with lung cancer in 2020 and there were 1.8 million deaths from this disease (Globocan 2020). The number of new lung cancer cases is expected to grow by about 70% over the next 2 decades (Globocan 2020). It is also the most common cause of death from cancer, with 1.8 million deaths representing 18.4% of the total deaths from cancer (Bray et al 2018). In 2019, approximately 142,670 deaths due to lung cancer are expected in the United States (US) (Siegel et al 2019) and 280,000 in the European Union (Malvezzi et al 2019). Despite apparently curative surgery, approximately 50% of stage IB and 70% of stage II NSCLC patients will relapse and eventually die of their disease. Given the current limited survival of patients with NSCLC, even in early stages of disease, new treatment options are needed. Neoadjuvant and adjuvant treatments are used to eradicate micrometastatic disease and minimize the risk of relapse.

A meta-analysis based upon seven trials involving 988 patients suggested that neoadjuvant chemotherapy (platinum-based chemotherapy-cisplatin or carboplatin, combined with other agents) improved OS in patients with NSCLC when given preoperatively (five-year survival 20% versus 14% without neoadjuvant chemotherapy). This improvement in survival is similar to that observed in the meta-analyses of predominantly adjuvant chemotherapy (Burdette-Radoux and Muss 2006, Scagliotti et al 2012, Chuang et al 2017). The neoadjuvant setting offers the possibility for the identification of surrogate clinical and biological markers that may correlate with response to therapy and in some cases long-term outcome. In addition, preoperative therapy may be a useful platform for the development of new targeted therapies. Efficient strategies to evaluate promising agents in early phase development are essential for rapid progress in lung cancer treatment and prevention. Several studies have shown preoperative systemic therapy to be safe prior to surgical resection of NSCLC with no difference in extent of surgical procedures performed, operative morbidity and mortality (Depierre et al 2002, Gilligan et al 2007, Scagliotti et al 2012).

Activating mutations in Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK) translocations are molecular drivers in NSCLC and their presence is strongly predictive of superior response to EGFR and ALK Tyrosine Kinase Inhibitors (TKIs) when compared to standard chemotherapy. For participants harboring EGFR activating mutations and ALK translocations, targeted therapies have become the standard of care (SoC) in both treatment-naive and pretreated participants (Ettinger et al 2010, Sequist et al 2013, Zhou et al 2011, Fukuoka et al 2011, Shaw and Engelman 2013, Shaw et al 2013, Rosell et al 2012, Solomon et al 2014, NCCN 2020). The success of EGFR and ALK TKIs highlights the importance of identifying specific molecular drivers of NSCLC and appropriately direct targeted agents to specific patient populations. Similarly, other TKIs directed at rare targets like ROS1 translocations and BRAF V600 mutations are now available for subsets of participants harboring these oncogenic drivers (Solomon et al 2014, Hamanishi et al 2016). The potential for prolonged and meaningful clinical response, by targeting these oncogenic drivers, delays the need for chemotherapy or other treatments.

In human cancer, the MET pathway is frequently dysregulated, triggering a diverse set of signaling cascades (including the RAS-MAPK as well as the PI3K-AKT pathway), which

promote proliferation, survival, motility and angiogenesis of tumor cells (Christensen et al 2005). Several mechanisms have been identified through which the MET pathway becomes aberrantly activated in cancer, including MET exon 14 skipping (METex14) mutations, MET gene amplification, chromosomal rearrangements leading to MET fusion proteins, MET receptor overexpression, and autocrine or paracrine activation of MET by its ligand Hepatocyte Growth Factor (HGF). METex14 mutations and MET amplification are currently the most studied MET dysregulations in NSCLC, being evaluated as predictors of response to MET inhibitors.

The presence of METex14 mutations leads to loss of the juxtamembrane domain of the receptor, which causes protein stabilization and oncogenic activation (Kong-Beltran et al 2006). Next generation sequencing of tumor specimens has identified many different variants resulting in exon 14 skipping. These variants are rare and collectively found at a frequency of 2-4% in lung cancer (Frampton et al 2015, Schrock et al 2016, Schrock et al 2016). Recent clinical observations suggest that such mutations are predictors of response to capmatinib and other MET targeting agents (Frampton et al 2015, Paik et al 2015, Jenkins et al 2015, Mendenhall and Goldman 2015, Waqar et al 2015, Liu et al 2015, Schuler et al 2016, Drilon 2016, Cedrés et al 2018, Wolf et al 2018).

In NSCLC, MET dysregulation has been found to be a negative prognostic factor (Guo et al 2014, Landi et al 2017, Awad et al 2019), particularly when both MET amplification and mutation occur in the same tumor (Awad et al 2019). Activation of the MET pathway is associated with many cancers and can be caused by MET exon 14 skipping mutation (METex14), overexpression and gene amplification. METex14 occur in 3–4% and MET amplifications in 1–6% of patients with NSCLC (Paik et al 2015, Saigi et al. 2018, Guo et al. 2019). Subsequent treatment options are limited, because MET mutations are known to be mutually exclusive of other established oncogenic molecular drivers in NSCLC and mostly occur in elderly participants (more than two-thirds > 65 years) (Schrock et al 2016), in whom triplet combinations of platinum doublet and IO may often not be feasible due to poor tolerability compared to younger participants with less comorbidities. In addition, participants with MET exon14 mutated NSCLC appear to have a relatively higher incidence of BM that in the general NSCLC population (up to 40%) (Wolf et al 2018, Awad et al 2019, Awad et al 2019).

There have been promising efficacy data in clinical studies with MET inhibitors, including capmatinib, in participants whose tumors harbor METex14 mutations, confirming the value of this class of mutations in predicting the response to targeted therapies directed against MET.

The GEOMETRY mono-1 study was a multiple-cohort, phase 2 study evaluating capmatinib in 364 patients with *MET*-dysregulated advanced NSCLC. Patients were assigned to cohorts on the basis of previous lines of therapy and *MET* status (*MET* exon 14 skipping mutation or *MET* amplification according to gene copy number in tumor tissue. Among patients with NSCLC with a *MET* exon 14 skipping mutation, overall response was observed in 41% (95% confidence interval [CI], 29 to 53) of 69 patients who had received one or two lines of therapy previously and in 68% (95% CI, 48 to 84) of 28 patients who had not received treatment previously; the median duration of response was 9.7 months (95% CI, 5.6 to 13.0) and 12.6 months (95% CI, 5.6 to could not be estimated), respectively. Limited efficacy was observed in previously treated patients with *MET* amplification who had a gene copy number of less than 10 (overall response

in 7 to 12% of patients). Among patients with *MET* amplification and a gene copy number of 10 or higher, overall response was observed in 29% (95% CI, 19 to 41) of previously treated patients and in 40% (95% CI, 16 to 68) of those who had not received treatment previously. The most frequently reported adverse events were peripheral edema (in 51%) and nausea (in 45%); these events were mostly of grade 1 or 2. Capmatinib is approved for targeted therapy for participants with METex14 mutated NSCLC tumors (Frampton et al 2015, Jenkins et al 2015, Liu et al 2016, Mendenhall and Goldman 2015, Paik et al 2015, Waqar et al 2015, Drilon 2016, Schuler et al 2016, Wolf et al 2017, Wolf et al 2018, Wolf et al 2019).

1.2 Purpose

Activation of the MET pathway is associated with many cancers and can be caused by MET exon 14 skipping mutation (METex14), overexpression and gene amplification. METex14 occur in 3–4% and MET amplifications in 1–6% of participants with NSCLC (Paik et al 2015, Saigi et al. 2018, Guo et al. 2019). Capmatinib is approved in the United States for the treatment of metastatic NSCLC with METex14 mutation and has an adverse event profile that is manageable and not expected to complicate surgery (Wolff et al. 2019, Paik et al 2020). The current study will determine if neoadjuvant capmatinib can improve the major pathological response (MPR) in participants with stages IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) lung cancers with MET exon 14 mutations and/or high MET amplification beyond those achieved with surgery, chemotherapy, and radiation. Treatment will continue with capmatinib in the adjuvant setting to evaluate the potential clinical benefit of extended therapy and allow longer follow up in order to assess disease free survival [redacted]

2 Objectives and endpoints

Objectives and related endpoints are described in Table 2-1 below.

Table 2-1 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint(s) for primary objective(s)**
To determine the MPR in resection specimens following neoadjuvant capmatinib in 2 cohorts. Cohort A: MET exon 14 skipping mutation, irrespective of MET GCN; Cohort B: High MET amplification (MET: GCN ≥ 10)	MPR rate in each cohort based on local review, defined as the percentage of participants with ≤ 10% residual viable cancer cells
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
To assess overall response rate post neoadjuvant treatment with capmatinib in each cohort	Overall response rate (ORR) based on local investigator assessment per RECIST 1.1
To determine the complete pathologic response following neoadjuvant capmatinib therapy in each cohort	Complete pathologic response (pCR) rate based on local review
To evaluate safety and tolerability of capmatinib	Type, frequency and severity of AEs [CTCAE] v5.0), vital signs and laboratory abnormalities

Objective(s)	Endpoint(s)
To assess disease free survival with adjuvant therapy with capmatinib	Disease free survival rate at 24, 36, and 60 months

[redacted]

2.1 Primary estimand(s)

The following are scientific questions for both the two cohorts:

The primary scientific question of interest is to determine if neoadjuvant treatment effect of capmatinib followed by surgical resection and adjuvant treatment effect of capmatinib can improve clinical outcome, major pathological response (MPR) in patients with IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) lung cancers with MET exon 14 mutations and/or high MET amplification, regardless of study treatment discontinuation, beyond those achieved with surgery, chemotherapy, and radiation and before start of any new anti-neoplastic therapy.

The justification for targeting this treatment effect for both Cohort A and Cohort B is that it will enable us to evaluate the MPR even after treatment is discontinued, but avoid potential confounding effects of any other therapies or any new anti-neoplastic therapy.

For more detailed definitions, please refer to the Section 12.4.2.

The primary estimand is characterized by the following attributes:

1. Population: Newly diagnosed participants with clinical stages IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) lung cancers with MET exon 14 mutations and/or high level MET amplification (MET: GCN ≥ 10).
2. Treatment: Capmatinib (INC280) in the neoadjuvant and adjuvant setting at a dose of 400 mg b.i.d (tablets for oral use).
3. Variable: Major pathologic response (**MPR**) rate, defined as the proportion of evaluable participants with ≤ 10% residual viable cancer cells. MPR rate will be assessed in each cohort via local review for primary analysis.
4. Intercurrent events: The intercurrent events of interest are:
   - The treatment discontinuation for any reason: Tumor assessment data collected irrespectively of treatment discontinuation until start of antineoplastic therapy will be included to derive MPR (composite strategy).
   - Start of any other antineoplastic therapy: If any other antineoplastic therapy is taken, any subsequent assessment will be excluded from the MPR assessment (hypothetical strategy).
   - Any public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster (treatment policy strategy)

Details on how to handle the intercurrent events and strategy applied are provided in Section 12.4.3

5. S**ummary measure:** proportion of subjects with MPR.

2.2 Secondary estimands

No secondary estimands planned in this study.

3 Study design

This is a phase II, two-cohort, two-stage, study of capmatinib given for 8 weeks (2 cycles) prior to surgical resection, followed by three years capmatinib treatment in adjuvant setting. Surgery should be performed up to 2 weeks after the last dose of neoadjuvant study treatment. Please contact the sponsor if surgery will be beyond the 2 week window.

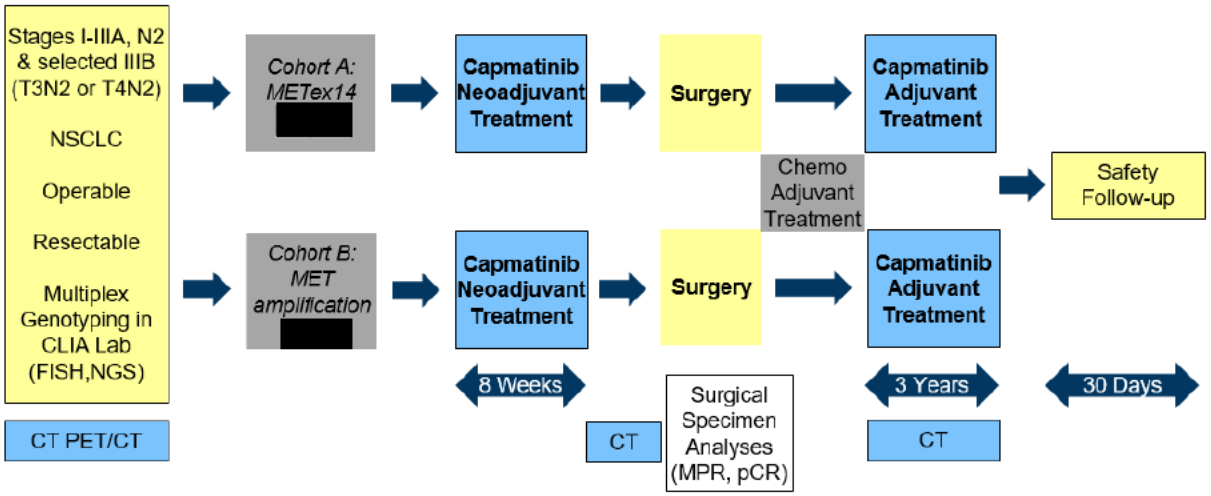
There will be 2 molecularly defined cohorts enrolling in parallel: Cohort A: MET exon 14 skipping mutations, irrespective of MET GCN or Cohort B: high level MET amplification (MET: GCN ≥10 by FISH or FoundationOne CDx NGS using tumor tissue). [redacted] Participants who have both MET exon 14 skipping mutations and high level

MET amplification (MET: GCN ≥10 by FISH or FoundationOne CDx NGS using tumor tissue) will be enrolled into Cohort A. An evaluable subject will undergo the neoadjuvant treatment and undergo surgery with a pathological response report analysis.

[redacted]

After surgery, participants will continue onto 3 years of adjuvant capmatinib therapy, followed by two years of survival follow-up.

Figure 3-1 Study design



*Adjuvant chemotherapy is optional and at the discretion of the treating physician. See section 6.2.1.2 for further details.

4 Rationale

4.1 Rationale for study design

An estimated 2.2 million people were diagnosed globally with lung cancer in 2020 and there were 1.8 million deaths from this disease (Globocan 2020). In the United States, lung cancer occurs in approximately 230,000 participants with 135,000 deaths each year. Lung cancer causes more deaths than breast, prostate, colorectal, and brain cancers combined (Siegel 2020). Surgery is the treatment of choice in participants with operable stage I – IIIA NSCLC. Neoadjuvant cisplatin-based chemotherapy improves both survival and cure (5-year disease-free survival) in unselected participants with stages IB-IIIA lung cancers to a degree at least equal to adjuvant use of the same chemotherapies. Rates of complete pathologic response are

5-10% and major pathologic response 11-20% with cisplatin-based chemotherapy (Group NM-aC, 2014). Neoadjuvant therapy in lung cancers has several advantages over adjuvant therapy, most importantly the ability to assess effectiveness of interventions early and to use surgical findings as an indicator of long-term outcomes and to guide postoperative therapies (Hellmann et al 2014, Blumenthal et al 2018).

In participants with breast cancers, neoadjuvant approaches have become a common strategy that can provide *better* outcomes over adjuvant therapy. Trials have demonstrated that pathologic complete response rates correlate with overall survival. Because of the correlation, the FDA has accepted neoadjuvant pathologic complete response as an endpoint for the approval of new drugs. This strategy can markedly shorten the time and costs involved in new drug development and adjuvant trials.

Adjuvant therapy for patients with stage II or III NSCLC has shown improved survival based on the results from large randomized trials and meta-analyses (Pignon et al 2008, Winton et al 2005). Therapies to further improve the clinical outcomes of patients with stage I-III NSCLC are still needed.

4.2 Rationale for dose/regimen and duration of treatment

Based on the PK and safety data, capmatinib 400 mg b.i.d. in tablet formulation has been declared the recommended phase II dose (RP2D) [CINC280X2102]. Furthermore, robust efficacy has been demonstrated in both 2/3L and 1L MET mutant NSCLC participants at this dose level, in which brain activity has been observed [CINC280A2201]. [redacted] This dose demonstrated robust clinical efficacy and safety and has been approved in the US for market authorization (Wolf et al 2020). Therefore, this dose was chosen for the current study.

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

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

See Section 12.7.

4.5 Risks and benefits

The participants enrolled in this study will have stage IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) lung cancers who are amenable to surgery. Given the clinical and molecular characteristics of METex14 mutated or high level MET mutation NSCLC, participants have fewer therapeutic options, and the established SoC has limited benefit in this participant population.

Appropriate eligibility criteria, as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced AEs are provided in Section 6.5.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, and, as with any clinical study, there may be unforeseen risks with the study treatment, which could be serious. The specific risks for capmatinib are discussed below. [redacted]

Women of childbearing 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.

4.5.1 Capmatinib

Based upon the clinical experience with capmatinib to date, the overall risk-benefit assessment of capmatinib is considered favorable. The data of study [INC280A2201] show that capmatinib is generally well tolerated and has a manageable safety profile. The safety profile in the METex14 mutated NSCLC population is consistent with the safety profile of capmatinib across multiple clinical studies. In the context of the significant clinical benefit observed for this participant population with limited effective therapeutic options, the overall safety profile is acceptable, and the benefit/risk favorable.

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

In addition, pancreatic events (e.g. amylase and lipase increase), and liver function test alterations (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) and/or bilirubin increase) have been observed in participants treated with capmatinib. To date, a direct toxic effect of capmatinib on pancreas cannot be definitively identified. Caution is recommended when capmatinib is administered in combination with other drugs with a known risk of hepatotoxicity. Pneumonitis and Interstitial Lung Disease (ILD) have been reported from both capmatinib single agent and combination studies with EGFR TKIs, including events with fatal outcomes. Investigators are advised to carefully monitor participants for signs and symptoms of pneumonitis and implement dose modification and follow-up evaluations described in the protocol in all capmatinib studies, both single agent and in combination studies.

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

[redacted]

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 the Public health emergency should be discussed

with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

Newly diagnosed participants with clinical stages IB-IIIA and select IIIB lung cancers with MET exon 14 mutations and/or high level MET amplification (MET: GCN ≥ 10). The presence of MET exon 14 mutations can be determined by any assay conducted in a CLIA certified laboratory. High level MET amplification can be determined by FISH in a CLIA certified laboratory or FoundationOne CDx NGS (other NGS-based methods without adjusting for tumor content % cannot be accepted). All participants will be deemed to be both operable and resectable by the thoracic surgeon who will perform surgery upon completion of neoadjuvant capmatinib.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Adult ≥ 18 years of age at the time of informed consent.
3. Histologically confirmed NSCLC stage IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) (per AJCC 8th edition), deemed suitable for primary resection by treating surgeon (T4 tumors with mediastinal organ invasion are not eligible for enrollment).
4. Participant must have MET exon 14 mutation and/or high level MET amplification (MET: GCN ≥ 10) as determined by a CLIA certified laboratory. High level MET amplification must be identified by FISH in a CLIA certified laboratory or FoundationOne CDx NGS (other NGS-based methods without adjusting for tumor content % cannot be accepted).
5. Participants must be eligible for surgery and scheduled for surgical resection within approximately 2 weeks after the last dose of neoadjuvant study treatment.
6. Participants must have adequate organ function including the following laboratory values at the screening visit:
    - 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) ≥ 45 mL/min
    - Total bilirubin (TBIL) ≤ 1.5 ULN (upper limit of normal)
    - Aspartate transaminase (AST) ≤ 3 x ULN
    - Alanine transaminase (ALT) ≤ 3 x ULN
    - Asymptomatic serum amylase ≤ 5 x ULN (Grade 2). Participants with Grade 1 or Grade 2 serum amylase at the beginning of the study must be confirmed to have no signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g. elevated P-amylase, abnormal imaging findings of pancreas, etc.)
    - Serum lipase ≤ ULN

- Alkaline phosphatase (ALP) ≤ 5.0 x ULN

7. Participant must have adequate cardiovascular and respiratory function to be submitted to surgical procedure as assessed per local clinical practice, including:
   - Adequate pulmonary function to be eligible for surgical resection. Postoperative predicted forced expiratory volume in 1 second (FEV1) and diffusion capacity must be ≥ 40% and/or maximal oxygen consumption (VO2 max) should be > 10 mL/kg/min.
8. ECOG PS of 0 or 1.
9. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.
10. Participants must have a life expectancy of at least 3 months.

5.2 Exclusion criteria

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

1. Participants with unresectable or metastatic disease. All participants should have brain imaging (either MRI brain or CT brain with contrast) prior to enrollment to exclude brain metastasis.
2. Presence or history of a malignant disease that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
3. Prior treatment with any MET inhibitor or HGF-targeting therapy.
4. Participants with other known oncogenic driver alterations.
5. History of or current interstitial lung disease or pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
6. Clinically significant, uncontrolled heart disease and/or recent cardiac event, such as:
   - Unstable angina or myocardial infarction within 6 months prior to screening
   - History of documented congestive heart failure (CHF) (New York Heart Association functional classification III-IV)
   - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening. 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
   - QTcF ≥ 470 ms on the screening ECG (as mean of triplicate ECG)
7. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to starting study treatment, or who have not recovered from side effects of such procedure. Video- assisted thoracic surgery (VATS) and mediastinoscopy for diagnostic and/or

staging purposes will not be counted as major surgery and participants can be enrolled in the study ≥1 week after the procedure.

8. Participants receiving treatment with strong inducers of CYP3A and cannot be discontinued at least 1 week prior to the start of treatment and for the duration of the study.
9. Prior systemic anti-cancer therapy (chemotherapy, immunotherapy, biologic therapy, vaccine) or investigational agents for NSCLC within the past 3 years.
10. Impairment of GI function or GI disease that may significantly alter the absorption of capmatinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
11. Unable or unwilling to swallow tablets as per dosing schedule
12. Participants receiving unstable or increasing doses of corticosteroids. 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 first dose of capmatinib.
13. Participants receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of capmatinib, and for the duration of the study. Participants on non-enzyme-inducing anticonvulsants are eligible.
14. 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.
15. Participants with known hypersensitivity to capmatinib and any of the excipients of capmatinib (crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes).
16. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome.
17. Any other condition that would, in the Investigator's judgment, contraindicate participant's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., active infection (including active hepatitis B and C, SARS-CoV-2), inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.
18. Pregnant or nursing (lactating) women.
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective contraception during the study and for 7 days after stopping treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment

- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient
- Use of oral, injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before study entry. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by laboratory assessment is she considered not of childbearing potential. Medical documentation of oophorectomy, hysterectomy, or bilateral tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

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

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

When non-child-bearing potential status is determined during the study, further pregnancy testing will not be continued. If local requirements dictate otherwise, local regulations should be followed.

20. Sexually active males unless they use a condom during intercourse while taking drug and for 7 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen

6 Treatment

6.1 Study treatment

The investigational drug to be used in this study is capmatinib, as described in Table 6-1. The study treatment is defined as capmatinib administered orally as a single agent.

Capmatinib will be labeled and provided to sites by Novartis in compliance with US regulations.

6.1.1 Investigational drug

The study treatment begins on Cycle 1 Day 1 with the first administration of capmatinib. All dosages prescribed and dispensed to the participant and all dose changes during the study must

be recorded on the dose administration electronic Case Report/Record Form (eCRF). Refer to Section 6.7.2 for study drug prescribing and administration information.

Table 6-1 Investigational and control drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Capmatinib (INC280) 150 mg or 200 mg	Film-coated tablet	Oral use	Open-label bottles	Sponsor (local)

6.1.2 Supply of study treatment

Capmatinib 150 mg or 200 mg will be supplied by the sponsor (Novartis).

Storage conditions are described in the medication label. Medication labels will comply with the legal requirements of the country and be printed in the local language.

During the COVID-19 pandemic that limits or prevents on-site study visits, delivery of IMP directly to a participant's home is generally permitted 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. Implementation will need to be discussed with Novartis. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3-months supply. In this case, regular phone calls or virtual contacts (every 4 weeks or less frequently) will occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant´s health status until the participants can again visit the site.

6.1.3 Treatment group

All participants in this study will be treated with capmatinib 400 mg orally b.i.d.

A complete cycle of treatment is defined as 28 days of continuous capmatinib treatment.

Participants will be assigned to each cohort based on their biomarker status (either METex14 or high level MET amplification or both). See Section 3 for cohort definitions.

6.1.4 Guidelines for continuation of treatment

For guidelines on the management of common capmatinib associated toxicities and dose modification instructions see Section Section 6.5

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

6.1.5 Treatment duration

Participants will continue to receive study treatment for a maximum of three years following surgery or until early discontinuation (see Section 9.1.1). All participants must have an EOT & Safety follow-up visit per the assessment schedule, Table 8-1.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

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

The participant must be told to notify the investigational site about any new medications he/she takes after 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 drug through 30 days after the last dose of study drug 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, corticosteroid use will be documented on the appropriate eCRF until disease progression (as determined by investigator and confirmed by BIRC). Please refer to Section 9.2.

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 with exception to adjuvant chemotherapy per Section 6.2.1.1
- No radiotherapy should be given to participants

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

- Oral or topical antibiotics
- Medications to prevent or treat nausea, vomiting or diarrhea
- Oxygen therapy and blood products or transfusions
- Nutritional support or appetite stimulants
- Pain medication

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

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject is enrolled into the study must be recorded in the appropriate eCRF.

6.2.1.1 Adjuvant chemotherapy

Standard postoperative adjuvant chemotherapy, consisting of a platinum-based doublet for 4 cycles is allowed. For patients receiving adjuvant chemotherapy no more than 26 weeks can elapse between surgery and start of adjuvant capmatinib.

Chemotherapy regimen, dosing, start and stop dates must be recorded in the eCRF.

6.2.1.2 Permitted concomitant therapy requiring caution and/or action

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

- **Strong CYP3A inhibitors**: Co-administrating capmatinib with strong CYP3A inhibitor (itraconazole) increased capmatinib AUC_{inf} by 42%. There was no change in capmatinib C_{max}. Closely monitor participants for adverse reactions during coadministration of capmatinib with strong CYP3A inhibitors.
- **Moderate CYP3A inducers**: Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that coadministration of capmatinib with the moderate CYP3A inducer efavirenz (600 mg once daily for 20 days) would result in a 44% decrease in capmatinib $AUC_{0\text{-}12h}$ and 34% decrease in C_{max} at steady-state compared to administration of capmatinib alone. Caution should be exercised during concomitant use of capmatinib with moderate CYP3A inducers. Use an alternative medication with no or minimal potential to induce CYP3A during coadministration with capmatinib.
- **Certain CYP1A2 substrates with narrow therapeutic index (NTI)**: Capmatinib is a moderate CYP1A2 inhibitor. Coadministration of capmatinib increased sensitive CYP1A2 probe substrate (caffeine) AUCinf 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 inhibitors**: Coadministration of capmatinib with proton pump inhibitor (rabeprazole) decreased capmatinib AUC_{inf} by 25% and C_{max} by 38%. Exercise caution during concomitant use of capmatinib with proton pump inhibitors.
- **H_2-receptor antagonists and antacids**: As an alternative to proton pump inhibitors, an H_2-receptor antagonist or antacid can be taken. Capmatinib should be administered at least 3 hours before or 6 hours after an H_2-receptor antagonist. Capmatinib should be administered at least 2 hours before or 2 hours after an antacid.

Refer to Table 16-1 for a list of the medications that require caution when concomitantly used with capmatinib. If a medication listed in Section 16.1 appears on both the list of prohibited

and the list of medications to be used with caution (Table 16-1 and Table 16-2), the medication is prohibited.

6.2.2 Prohibited medication

During the course of the study, participants must not receive other antineoplastic therapies (e.g. investigational drugs, devices, chemotherapy, immunotherapies) or any other therapies that may be active against cancer with exception to adjuvant chemotherapy per Section 6.2.1.1.

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

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

Capmatinib: prohibited medication

Strong CYP3A inducers: Co-administration of capmatinib with strong CYP3A inducer (rifampicin) decreases capmatinib AUCinf by 67% and Cmax by 56% [CINC280A2102], which may decrease capmatinib anti-tumor activity. Therefore, concurrent use of strong CYP3A inducers are prohibited.

Additionally, 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.

Capmatinib prohibited medications are listed in Table 16-2.

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 first enrolled for pre-screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the ICF, the participant is assigned to the next sequential participant No. available to the investigator through the Clinical Data Management System interface. Once assigned, the Participant No. must not be reused for any other participant and the Participant No. for that individual must not be changed.

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.

6.3.2 Treatment assignment

Participants will be assigned to a cohort based on their mutational status. All eligible participants will receive treatment with capmatinib.

All participants who fulfill all inclusion/exclusion criteria will be assigned to one of the cohorts of interest and information will be collected.

Cohort A

[redacted] Cohort A includes eligible participants with MET exon 14 skipping mutations. Participants who have both MET exon 14 skipping mutations and high level MET amplification (MET: GCN ≥10 by FISH or FoundationOne CDx NGS using tumor tissue) should be enrolled into Cohort A. Total enrollment to a cohort will depend on the decision to expand the cohort. See Section 3 for the study design.

Cohort B

[redacted] Cohort B will include eligible participants with high level MET amplification (MET: GCN ≥ 10). Total enrollment to a cohort will depend on the decision to expand the cohort. See Section 3 for the study design.

The study treatment phase begins on Cycle 1 Day 1 with the first administration of capmatinib. Cycle 1 Day 1.

6.4 Treatment blinding

This is an open-label study, therefore treatment assignment will be known to participants, investigator staff, persons performing the assessments, and the Novartis representatives from the Clinical Trial Team.

6.5 Dose modifications

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

Dose reductions are allowed for capmatinib and should follow the dose reduction steps described in Table 6-2 and Table 6-3. For each participant, a maximum of two consecutive dose level reductions is allowed after which the participant must be discontinued. Dose reductions of capmatinib below 200 mg b.i.d are not permitted. The lowest dose allowed, 200 mg b.i.d. in tablets is expected to be pharmacologically active, as the observed steady state plasma trough concentrations ([CINC280X1101], [CINC280X2202], n=6) were above the concentration associated with full MET inhibition in xenograft mice models (IC90, 120 nM total concentration).

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

Unless otherwise indicated in Table 6-3, for grade 1 and tolerable grade 2 treatment-related toxicities, participants may continue full doses of capmatinib. For intolerable grade 2 or grade 3 treatment-related toxicities, dosing should be interrupted until at least resolution to grade 1

followed by either dose reduction or re-initiation at the same dose level, depending on the type of toxicity as described in Table 6-3. For any grade 4 toxicity, except for neutropenia, febrile neutropenia, anemia and thrombocytopenia, participants should interrupt capmatinib until resolution to grade 1, followed by either dose reduction or treatment discontinuation (refer to Table 6-3).

Permanent treatment discontinuation is mandatory for specific events indicated in Table 6-3. Deviations to mandatory dose discontinuations are not allowed.

All interruptions or changes to study drug administration must be recorded in the dose administration eCRF.

Dose re/escalation of study treatment to previous dose level is allowed only once, and if no AE leading to dose modification is observed after at least 1 cycle (4 weeks) of study treatment at the reduced dose.

Any planned variance from the guidelines in Table 6-3, in view of participant safety (unless there is an urgent need for action) when in the opinion of the investigator the participant continues to experience clinical benefit, should first be discussed and approved by the Novartis Medical Lead or designee.

Events not included in the study protocol or the reference guidance documents should be managed according to local practices. All dose changes must be recorded on the appropriate eCRF.

Table 6-2 Dose reduction steps for capmatinib

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

Note: dose reduction should be based on the worst toxicity demonstrated at the last dose. Dose reduction below 200 mg is not allowed.

Table 6-3 Criteria for dose reduction / interruption and re-initiation/ permanent discontinuation of capmatinib treatment for adverse drug reactions

Dose modifications for capmatinib	
Worst toxicity CTCAE Grade[a]	**During a cycle of therapy**
No toxicity	Maintain dose level
HEMATOLOGICAL	
Neutrophil count decreased (ANC) Neutropenia	
Grade 1 (ANC < LLN - 1500/mm3; < LLN - 1.5 x 10^9/L)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm3; < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm3; < 1.0 - 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then: • If resolved in ≤ 7 days, resume treatment at the same dose level • If resolved in > 7 days, then ↓ 1 dose level

Grade 4 (ANC < 500/mm3; < 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level
Platelet count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75,000/mm3; < LLN - 75 x 10^9/L)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm3; < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm3; < 50 - 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm3; < 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then ↓1 dose level
Febrile neutropenia (ANC < 1000/mm3 (< 1.0 x 10^9/L), fever > 38.3°C)	Omit dose, then: • If resolved in ≤ 7 days, resume treatment at ↓ 1 dose level • If resolved in > 7 days, permanently discontinue participant from study drug treatment
Hemoglobin decreased (Anemia)	
Grade 1 (Hgb < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L)	Maintain dose level
Grade 2 (Hgb < 10.0 - 8.0 g/dL; < 6.2 – 4.9 mmol/L; < 100 - 80 g/L)	Maintain dose level
Grade 3 (Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L	Omit dose until resolved to ≤ grade 2, then: • If resolved in ≤ 7 days, resume treatment at the same dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level If toxicity recurs, permanently discontinue participant from study drug treatment.
RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at the same dose level.
Grade 3 (> 3.0 - 6.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at ↓ 1 dose level.
Grade 4 (> 6.0 x ULN)	Permanently discontinue participant from study drug treatment
HEPATIC	
Isolated Total bilirubin elevation*	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level

Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, ↓1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, ↓ 1 dose level • If resolved in > 7 days, permanently discontinue capmatinib
Grade 4 (> 10.0 x ULN)	Permanently discontinue participant from study drug treatment
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3 x ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 if grade 2 elevation at baseline) then: • If resolved in ≤ 7 days, then resume treatment at the same dose level • If resolved in > 7 days, resume treatment at ↓ 1 dose level
Grade 4 (> 20.0 x ULN)	Mandatory: Permanently discontinue participant from capmatinib treatment
Combined elevations of AST or ALT and Total bilirubin[b,d]	
For participants with normal baseline ALT and AST and TBL value: AST or ALT > 3.0 x ULN combined with TBL > 2.0 x ULN without evidence of cholestasis[c] Or hemolysis OR For participants with elevated baseline AST or ALT or TBL value: [AST or ALT > 3 x baseline] OR [AST or ALT > 8.0 x ULN], whichever is lower, **combined with** [TBL > 2 x baseline AND > 2.0 x ULN]	Mandatory: Permanently discontinue participant from study drug treatment
METABOLIC	
Amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN; > 2.0 - 5.0 x ULN and asymptomatic)	Maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms; > 5.0 x ULN and asymptomatic)	Omit the dose until resolved to ≤ grade 2, then • If resolved in ≤ 14 days, resume treatment at the same dose level • If resolved in > 14 days, then ↓ 1 dose level
Grade 4 (> 5.0 x ULN and with signs or symptoms)	Permanently discontinue participant from study drug treatment
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTcF 450-480 ms) and	Maintain dose level

Grade 2 (QTcF 481-500 ms)	
Grade 3 (QTcF ≥ 501 ms on at least two separate ECGs)	Omit dose until resolved to ≤ grade 2, then: • If resolved in ≤ 7 days, resume treatment at the same dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (QTcF ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue participant from study drug treatment
GASTROINTESTINAL	
Pancreatitis	
Grade 2	Maintain dose level
Grade ≥ 3	Permanently discontinue participant from study drug treatment
Diarrhea**	
Grade 1 (despite maximal anti-diarrheal medication)	Maintain dose level
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then maintain dose level. • If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then resume treatment at↓ 1 dose level
Grade 3 or 4 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Vomiting	
Grade 1 (despite appropriate anti-emetics)	Maintain dose level
Grade 2 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then maintain dose level. • If vomiting returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Nausea	
Grade 1 or 2 (despite appropriate anti-emetics)	Maintain dose level
Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Rash/photosensitivity***	
Grade 1	Maintain dose level.
Grade 2	Maintain dose level.
Grade 3, despite skin toxicity therapy	Omit dose until resolved to grade ≤ 1, then: • If resolved in ≤ 7 days, then resume treatment at ↓ 1 dose level

	• If resolved in > 7 days (despite appropriate skin toxicity therapy), then permanently discontinue participant from study drug treatment
Grade 4, despite skin toxicity therapy	Omit dose and permanently discontinue participant from study drug treatment
RESPIRATORY DISORDERS	
Interstitial Lung Disease (ILD) /Pneumonitis Monitor participants for pulmonary symptoms indicative of ILD/Pneumonitis. In addition, withhold capmatinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for ILD/Pneumonitis to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage.	
Grade 1	Interrupt capmatinib during diagnostic workup for ILD/Pneumonitis. Exclude infections and other etiologies. **In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib.** Only in absence of diagnosis of ILD/Pneumonitis, study drug may be restarted at the same dose. If it recurs after restarting of study drug, permanently discontinue capmatinib.
Grade 2	Mandatory: Interrupt capmatinib dose during diagnostic workup for ILD until improvement to ≤ Grade 1. Exclude infections and other etiologies. **In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib.** Only in absence of diagnosis of ILD/Pneumonitis, study drug may be restarted 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 recurs after resumption of study drug at decreased dose, permanently discontinue capmatinib
Grade 3 and Grade 4	Permanently discontinue study drug Treat with IV steroids as clinically indicated. Oxygen therapy as indicated.
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, resume treatment at same dose level • If resolved in > 7 days, resume treatment at↓ 1 dose level

Peripheral edema	
Grade 1 or 2	Maintain dose level
Grade 3	Discontinue dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue study drug
Other AEs	
Grade 1 or 2	Maintain dose level, consider to initiate appropriate support medication. For any intolerable grade 2 (e.g.: limiting instrumental ADL), consider omitting the dose until resolved to ≤ grade 1, then restart either at the same dose or ↓ 1 dose level.
Grade 3	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue study drug
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: TBL 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 TBL do not meet the defined thresholds, please follow the instructions for isolated elevation of TBL 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 TBL > 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.	

6.5.1 Treatment interruption and treatment discontinuation

If the administration of capmatinib is temporarily interrupted for reasons other than toxicity, then treatment with capmatinib may be resumed at the same dose. If the treatment with capmatinib is withheld due to toxicity, the dose modification guidelines in Table 6-3 & Table 6-2 should be followed. In any case, scheduled visits and all assessments (including tumor assessments) should continue to be performed, as described in Table 8-1.

If the treatment with capmatinib is withheld for more than 21 consecutive days (counting from the first day when a dose was interrupted), excluding the surgical and adjuvant chemotherapy

window specified below, then capmatinib should be permanently discontinued. Under exceptional circumstance, when the investigator believes that continuing treatment may still derive clinical benefit for the participant, study treatment may be resumed. However, the investigator must discuss and receive approval from Novartis Medical Lead or designee prior to continuing capmatinib treatment.

Participants who discontinue the study due to a study drug related AE or an abnormal laboratory value must be followed as described in Section 6.5.2.

After the 8 week neoadjuvant treatment with capmatinib, participants are to undergo surgical resection. Participants should undergo within 2 weeks after last dose of neoadjuvant capmatinib. In addition, participants may receive adjuvant chemotherapy prior to re-starting capmatinib at the discretion of the investigator. For patients who do not receive adjuvant chemotherapy no more than 10 weeks should elapse from the date of surgery and the start of adjuvant capmatinib. For patients who do receive adjuvant chemotherapy, see Section 6.2.1.1 for the dosing window. If participants for any reason cannot re-start capmatinib therapy within the specified windows, then study treatment must be permanently discontinued.

Participants who discontinue the study due to a surgery related AE must complete the EOT visit and safety follow-up visit.

6.5.2 Follow-up for toxicities

All participants will be followed for safety until 30 days after the last dose of capmatinib. Participants whose treatment is temporarily interrupted or permanently discontinued due to a toxicity AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

An unscheduled assessment should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments. Subsequent monitoring must be performed as per the regular visit schedule. Please refer to Table 6-4 for follow-up evaluations for selected toxicities.

Table 6-4 Follow-up evaluations for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION
HEMATOLOGICAL	
Febrile neutropenia, Neutropenia ≥ CTCAE grade 3 Thrombocytopenia ≥ CTCAE grade 3 Anemia ≥ CTCAE grade 3	• Test weekly (or more frequently if clinically indicated) until ≤ CTCAE grade 2. • Perform physical exam for check on bruising in case of major thrombocytopenia.
RENAL	
Serum creatinine ≥ CTCAE grade 2	• Test weekly (or more frequently if clinically indicated) until ≤ CTCAE grade 1 or baseline. • Participants will be instructed to increase hydration until resolution to ≤ CTCAE grade 1 or baseline.

TOXICITY	FOLLOW-UP EVALUATION
HEPATIC	
Isolated Total bilirubin elevation	TBL CTCAE Grade 1: • Monitor LFTs per protocol or more frequently if clinically indicated TBL CTCAE Grade 2: • Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN TBL 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 TBL have resolved to baseline or stabilization over 4 weeks TBL 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 TBL have resolved to baseline or stabilization over 4 weeks

Isolated AST/ALT elevation	• AST/ALT CTCAE Grade 2 elevation:
	  • For participants with baseline value ≤ 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
	  • For participants with baseline value > 3.0 x ULN: monitor LFTs per protocol or more frequently if clinically indicated
	• AST/ALT CTCAE Grade 3 elevation:
	  • For AST/ALT elevation > 5.0 - 10.0 x ULN:
	  • For participants with baseline value ≤ 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
	  • For participants with baseline value > 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs, weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN
	• For AST/ALT elevation > 10.0 - 20.0 x ULN:
	  • Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results;

TOXICITY	FOLLOW-UP EVALUATION
	monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ baseline • AST/ALT CTCAE Grade 4 elevation: • Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.

Combined AST or ALT and Total bilirubin elevation without cholestasis or hemolysis	• Combined elevations of AST or ALT and TBL:
	  • After discontinuing the participant from capmatinib permanently, repeat LFTs as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks.
	  • Core LFTs consist of ALT, AST, Gamma-glutamyl transferase (GGT), TBL (fractionated [direct and indirect], if TBL > 2.0 x ULN), and ALP (fractionated [quantification of isoforms], if ALP > 2.0 x ULN.)

METABOLIC	
Asymptomatic 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:
	  • 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 (LLN), correct with supplements to within normal limits.
	  • Review concomitant medication usage for the potential to prolong the QT-interval.
	  • Check compliance with correct dose and administration of capmatinib.
	  • Perform a repeat ECG within one hour of the first QTcF of ≥501 ms.
	  • If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once daily until the QTcF returns to < 501 ms.

TOXICITY	FOLLOW-UP EVALUATION

	• 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 ECG report shows a QTcF ≥ 501 ms (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. Conduct a manual read of the repeat ECG immediately, and the above guidance followed.

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

TOXICITY	FOLLOW-UP EVALUATION
	(e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity). • Individualized supportive and anti-emetic treatment should be initiated, as appropriate, at the first signs and/or symptoms of these AEs. In participants with vomiting, the participant should be monitored for signs of dehydration and instructed to take preventive measures against dehydration. • Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator's best judgment.
SKIN TOXICITY	
Rash and Photosensitivity	
CTCAE grade 1	Consider to initiate institute appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
CTCAE grade 2	Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids).
≥ CTCAE grade 3	Intensify appropriate skin toxicity therapy and monitor weekly or more frequently until resolved to grade ≤ 2
Peripheral edema	
CTCAE grade≤2	Consider to initiate conservative measures such as leg elevation, compression stockings, and dietary salt modification as clinically indicated.
CTCAE grade≥3	Initiate/intensify conservative measures
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
ILD/Pneumonitis	
CTCAE **Grade 1**	• CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression-re-image at least every 3 weeks • Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse oximetry recommended • Consultation of pulmonologist recommended
CTCAE **Grade 2**	• CT scan (high-resolution with lung windows) • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Pulmonary function tests [a] - if normal at baseline, repeat every 8 weeks • Bronchoscopy with biopsy and/or BAL recommended [c] • Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated) [b]

TOXICITY	FOLLOW-UP EVALUATION
CTCAE **Grade 3 and Grade 4**	• Computerized Tomography (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 hours)[b]. • If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication
[a] PFT (Pulmonary function tests) to include: diffusing capacity of lungs 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 haemorrhage, opportunistic infections, cell count + determination lymphocyte CD4/8 count where possible.	

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

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

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

- For participants with normal ALT and AST and TBL value at baseline: AST or ALT > 3.0 x ULN combined with TBL > 2.0 x ULN
- For participants with elevated AST or ALT or TBL value at baseline: [AST or ALT >3.0 x baseline] OR [ALT or AST > 8.0 x ULN], whichever is lower, combined with [TBL > 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 as 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, TBL, direct and indirect bilirubin, GGT, GLDH, prothrombin time (PT)/INR, ALP, 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, 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 (livertox.nih.gov/rucam.html).

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

Table 6-5 Follow up on potential drug-induced liver injury (DILI) cases

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, Hepatitis B Virus (HBV) DNA; anti-HCV, Hepatitis C Virus (HCV) RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & 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 CHF, 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 Stimulation Hormone (TSH); CVD / ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

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

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

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as 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

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.

Treatment 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.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described in Section 6.1.1

A unique medication number (sequence number) is printed on the study medication label per bottle, as well as a unique packaging control number (PCN) per batch/labeling operation.

6.7.1 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. [redacted]

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 the country. They will include storage conditions for the study treatment but no information about the participant except for the medication kit number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by

monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and if appropriate during the course of the study, the investigator will destroy all unused study treatment, packaging, drug labels, and provide a copy of the completed drug accountability log to the study monitor. If the investigator cannot destroy these items compliantly, they may be returned to the study monitor or to the Novartis address provided in the investigator folder at each site.

The study drugs supply can be destroyed locally at the site only if permitted by local regulations and authorized by Novartis.

6.7.2 Instruction for prescribing and taking study treatment

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

Capmatinib tablets will be administered orally on a continuous b.i.d. dosing schedule from Day 1 to Day 28 of each 28 day cycle. The starting dose of capmatinib will be 400 mg b.i.d (total daily dose = 800 mg) on a flat scale of mg/day and not individually adjusted by weight or body surface area. A complete cycle of treatment is defined as 28 days of b.i.d. treatment with capmatinib. The investigator must instruct the participant to take the study drug exactly as prescribed. All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the dose administration eCRF.

- Each dose of capmatinib is to be taken with a glass of water (at least 8 ounces - approximately 250 mL) and consumed over as short a time as possible (i.e. not slower than 1 tablet every 2 minutes)
- Participants should be instructed to swallow the tablets whole and not to chew them
- Capmatinib can be administered with or without food. The morning and the evening dose should be taken 12 (± 4) hours apart, although a 12-hour interval is highly recommended. The morning dose should be taken at the same time each morning. If a dose is not take within 4 hours of the planned dosing time, the missed dose should not be replaced
- Participants should be instructed not to make up for missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined when the full dose is not taken within 4 hours of the scheduled twice daily dosing. If that occurs, then the dose (or part of the remaining dose) should not be taken and dosing should restart with the next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose.
- During the whole duration of treatment with capmatinib, the participant is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, avoid sunbathing or using a solarium).

Table 6-6 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
Capmatinib (150 mg or 200 mg tablets)	400 mg orally (2x 200 mg tablets)	Twice daily (28 day cycles)

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

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

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

[redacted] This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. [redacted] 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:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment

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.

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

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who discontinue the treatment should be scheduled for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule. At this visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Each treatment cycle is 28 days. Screening evaluations should be performed within ≤ 28 days of Cycle 1 Day 1 (except for the pregnancy test which has to be performed within 72 hours before the first dose & PFTs which can occur within 3 months of starting neoadjuvant treatment). Laboratory assessments performed as part of the screening evaluations that are within 72 hours of the first dose of study treatment are not required to be repeated on the first day of dosing (Cycle 1 Day 1).

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of +/- 3 days is allowed for study procedures (including treatment administration). A window of +/- 7 days from the planned visit date is allowed for imaging evaluations. Note: if a treatment cycle is delayed at any time during the study, all study visits and safety and efficacy assessments should continue according to the appropriate number of calendar days measured from Day 1 of the previous cycle, or more often if clinically indicated.

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

Table 8-1 Assessment schedule

Period	**Screening**	**Treatment**		**Surgery**		**Treatment**		**Follow-up**	
Cycle		**Cycle 1**	**Cycle 2**			**Cycle 3 & beyond up to 3 years**			
Visit Name	**Screening**	**Treatment C1D1**	**Treatment C2D1**	**Surgery**	**Post-surgery**	**Treatment C3D1**	**Treatment C4D1 & beyond**	**EOT**	**30 day safety follow up**
Days/months	**-28 to -1**	**1**	**28**	**Within 2 weeks from last dose of capmatinib[6]**	**2 weeks from date of surgery[9]**	**10-26 weeks from surgery[3]**	**Every 3 months**	**when applicable**	**30 days post last dose of capmatinib**
Informed consent	X								
Demography	X								
MET status confirmation	X								
Inclusion / Exclusion criteria	X								
Medical history/current medical conditions	X								
Smoking history	X								

Period	**Screening**	**Treatment**		**Surgery**		**Treatment**		**Follow-up**	
Cycle		**Cycle 1**	**Cycle 2**			**Cycle 3 & beyond up to 3 years**			
Visit Name	**Screening**	**Treatment C1D1**	**Treatment C2D1**	**Surgery**	**Post-surgery**	**Treatment C3D1**	**Treatment C4D1 & beyond**	**EOT**	**30 day safety follow up**
Days/months	**-28 to -1**	**1**	**28**	**Within 2 weeks from last dose of capmatinib[6]**	**2 weeks from date of surgery[9]**	**10-26 weeks from surgery[3]**	**Every 3 months**	**when applicable**	**30 days post last dose of capmatinib**
Diagnosis, stage and grade of cancer	X								
Histopathology assessment, (squamous or non-squamous)	X								
Physical Examination	S	S	S		S	S	S	S	S
ECOG Performance status	X	X	X		X	X	X	X	X
Vital Signs	X	X	X		X	X	X	X	
Body Weight	X	X	X		X	X	X	X	
Body Height	X								

Period	**Screening**	**Treatment**		**Surgery**		**Treatment**		**Follow-up**	
Cycle		**Cycle 1**	**Cycle 2**			**Cycle 3 & beyond up to 3 years**			
Visit Name	**Screening**	**Treatment C1D1**	**Treatment C2D1**	**Surgery**	**Post-surgery**	**Treatment C3D1**	**Treatment C4D1 & beyond**	**EOT**	**30 day safety follow up**
Days/months	**-28 to -1**	**1**	**28**	**Within 2 weeks from last dose of capmatinib[6]**	**2 weeks from date of surgery[9]**	**10-26 weeks from surgery[3]**	**Every 3 months**	**when applicable**	**30 days post last dose of capmatinib**
Electrocardiogram (ECG)	X	X[2]		If clinically indicated				X	
Pulmonary function tests (PFT)	X[4]			X[5]	X				
Hematology blood sample	X	X	X		X	X	X	X	X
Chemistry blood sample	X	X	X		X	X	X	X	X
Coagulation panel	X		If clinically indicated						
Urinalysis (dipstick)	X	X	X			X	X		

Period	**Screening**	**Treatment**		**Surgery**		**Treatment**		**Follow-up**	
Cycle		**Cycle 1**	**Cycle 2**			**Cycle 3 & beyond up to 3 years**			
Visit Name	**Screening**	**Treatment C1D1**	**Treatment C2D1**	**Surgery**	**Post-surgery**	**Treatment C3D1**	**Treatment C4D1 & beyond**	**EOT**	**30 day safety follow up**
Days/months	**-28 to -1**	**1**	**28**	**Within 2 weeks from last dose of capmatinib[6]**	**2 weeks from date of surgery[9]**	**10-26 weeks from surgery[3]**	**Every 3 months**	**when applicable**	**30 days post last dose of capmatinib**
Prior/concomitant medications	X	X (Continuous from 28 days prior to starting treatment until 30 day safety follow-up or start of new antineoplastic medication (ANP), whichever is sooner)							
Non-drug therapies and procedures	X	X (Continuous from 28 days prior to starting treatment until 30 day safety follow-up or start of new antineoplastic medication (ANP), whichever is sooner)							
Adverse Events	X (Continuous until ≥ 30 days after the last dose of INC280)								
Serious Adverse Events	X (Continuous until ≥ 30 days after the last dose of INC280)								
Serum pregnancy test	S (within 72 hours prior to first dose)							S[11]	S[11]
Urine pregnancy test[11]			S			S	S		

Period	**Screening**	**Treatment**		**Surgery**		**Treatment**		**Follow-up**	
Cycle		**Cycle 1**	**Cycle 2**			**Cycle 3 & beyond up to 3 years**			
Visit Name	**Screening**	**Treatment C1D1**	**Treatment C2D1**	**Surgery**	**Post-surgery**	**Treatment C3D1**	**Treatment C4D1 & beyond**	**EOT**	**30 day safety follow up**
Days/months	**-28 to -1**	**1**	**28**	**Within 2 weeks from last dose of capmatinib[6]**	**2 weeks from date of surgery[9]**	**10-26 weeks from surgery[3]**	**Every 3 months**	**when applicable**	**30 days post last dose of capmatinib**
Surgery				X					
PET-CT (with diagnostic quality CT)	X[10]								
CT/MRI – Chest	X[10]			X, To be performed within 7 days prior to surgery	X, At the initiation of adjuvant therapy (chemotherapy or capmatinib) and every 12 weeks for the first year of treatment, every 26 weeks thereafter[7]				
Brain MRI	X		If clinically indicated						
Whole body bone scan		If clinically indicated							
Tumor sample from surgery[1]				X					

Period	**Screening**	**Treatment**		**Surgery**		**Treatment**		**Follow-up**	
Cycle		**Cycle 1**	**Cycle 2**			**Cycle 3 & beyond up to 3 years**			
Visit Name	**Screening**	**Treatment C1D1**	**Treatment C2D1**	**Surgery**	**Post-surgery**	**Treatment C3D1**	**Treatment C4D1 & beyond**	**EOT**	**30 day safety follow up**
Days/months	**-28 to -1**	**1**	**28**	**Within 2 weeks from last dose of capmatinib[6]**	**2 weeks from date of surgery[9]**	**10-26 weeks from surgery[3]**	**Every 3 months**	**when applicable**	**30 days post last dose of capmatinib**
MPR				X					
Adjuvant chemotherapy[8]					X				
Study drug administration (capmatinib)		X (continuous twice daily (BID) dosing)				X (continuous twice daily (BID) dosing)			
Antineoplastic therapies since discontinuation of study treatment									X

X = assessment to be recorded in the clinical database or received electronically from a vendor

S = assessment to be recorded in the source documentation only

[1] Lymph nodes might be requested if collected, see Table 8-6 for number of unstained slides.

[2] pre-dose

[3] No more than 26 weeks or 10 weeks can elapse between surgery and start of adjuvant capmatinib for patients who have or have not received adjuvant chemotherapy, respectively.

[4] Within 3 months before starting neoadjuvant capmatinib

[5] After neoadjuvant capmatinib but before surgery

[6] Delay to the surgical procedure beyond 2 weeks is acceptable, but should be avoided. Please contact the sponsor if surgery will be beyond the 2 week window.

[7] Post-surgery scan schedule to start with initiation of any adjuvant treatment, chemotherapy or capmatinib.

[8]Standard postoperative adjuvant chemotherapy, consisting of a platinum-based doublet for 4 cycles is allowed. No more than 26 weeks can elapse between surgery and start of adjuvant capmatinib.

[9] Post-surgery visit to be approximately 2 weeks from date of surgery in alignment with practice guidelines.

[10] Chest CT/MRI or PET-CT (with diagnostic quality CT) is required at baseline.

[11] For women of child-bearing potential only

A visit window of +/- 3 days is allowed for study procedures (including treatment administration). A window of +/- 7 days from the planned visit date is allowed for imaging evaluations

8.1 Screening

Molecular pre-screening

Eligible participants must have METex14 mutation and/or high level MET amplification (MET: GCN ≥ 10) determined by a CLIA certified laboratory from formalin fixed, paraffin-embedded human tissue. Participant's METex14 mutation will be determined locally at a CLIA-certified laboratory compliant with LCMC4 master screening protocol. High level MET amplification (MET: GCN ≥ 10) must be determined by FISH in a CLIA certified laboratory or FoundationOne CDx NGS. Other NGS-based methods for determining gene copy number without adjusting for tumor content % are currently not accepted. Confirmation by a Novartis-designated central laboratory is not required to confirm eligibility prior to enrollment. Molecular pre-screening results will be captured in the eCRF.

Screening

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

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

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

8.1.1 Eligibility screening

The investigator is responsible to ensure only participants who meet all inclusion and do not meet any exclusion criteria are included in the study.

Participant eligibility will be checked by the sponsor once all screening procedures are completed. The eligibility check form will be sent from the site to the sponsor via email for evaluation. Upon confirmation of eligibility, the sponsor will return the signed eligibility check form via email to the site. The investigator site will then be allowed to start treatment to the participant.

8.1.2 Information to be collected on screening failures

Participants who sign an ICF and subsequently found to be ineligible prior to start of treatment will be considered a screen failure. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the subject experienced a SAE during the screening phase (see SAE section for reporting details). If a screen failure experiences AEs that are not SAEs will be followed by the investigator and collected only in the source data. If the subject fails to be enrolled, the sponsor must be notified within 2 days of the screen fail via e-mail that the subject did not initiate treatment.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed. In case of re-screening, a new participant ID will be generated, however, site has to provide original participant ID in respective eCRF to link the two participants for reporting and validation. All required screening activities must be performed when the participant is re- screened for participation in the study. An individual participant may only be re-screened once for the study. Once the number of participants screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the participants who screen failed will not be permitted to re-screen.

Participants who are enrolled and fail to start treatment, e.g. participants enrolled 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

Participant demographic and baseline characteristic data are to be collected on all participants. Relevant medical history/current medical conditions present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the appropriate eCRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature.

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, prior and current concomitant medications, prior antineoplastic therapies (medications, radiation, surgeries)
- Cancer characteristics including diagnosis, history, extent of cancer, MET mutation status, prior antineoplastic therapies (medications, radiation, surgeries).
- Tumor imaging assessments
- Other assessments to be completed for the purpose of determining eligibility (ECOG performance status, complete physical examination [only recorded in source documentation], vital signs, height, weight, hematology, blood chemistry, coagulation

studies, urinalysis, serum pregnancy test [only recorded in source documentation], and 12-Lead ECG)
- Pulmonary function tests
- Prior and current concomitant medications and surgical and medical procedures

8.3 Efficacy

8.3.1 Efficacy assessments

Major Pathological Response (MPR)

Response will be assessed locally at the time of surgery (by number of subject with ≤10% residual viable tumor cells). MPR assessment in tumor samples will be collected at time of resection**.** MPR rate as assessed by the number of participants with ≤ 10% residual viable cancer cells and will be assessed locally. In addition, the local MPR assessment will be confirmed centrally. All formalin-fixed, paraffin embedded (FFPE) tumor tissues collected at surgery must be submitted, detailed instructions for sample collection and processing will be included in the central lab manual.

Radiologic

The following assessments are required at screening/baseline:
- Chest CT/MRI or PET-CT (with diagnostic quality CT)
- Brain MRI/CT
- Whole body bone scan, if clinically indicated

In the neoadjuvant setting 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) and within 7 days prior surgery. See Table 8-1. Tumor response will be assessed locally based on RECIST 1.1.

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

In the adjuvant setting imaging assessments will begin with the initiation of any adjuvant treatment, chemotherapy or capmatinib, and are to be performed every 12 weeks for the first year of treatment and then every 26 weeks thereafter during adjuvant treatment. First disease recurrence must be radiologically confirmed by the investigator. In case of non-conclusive radiological evidence, a biopsy should be performed to confirm recurrence. If a biopsy is not feasible, the subject will be followed up until recurrence can be confirmed as per protocol (radiologically conclusive and/or biopsy). **The intervals between imaging assessments across all study phases should be respected as described above regardless of whether study treatment is temporarily withheld or if unscheduled assessments are performed.** A window of ±7 days is permitted is permitted to take into account scheduling over holidays.

For any antineoplastic therapy, surgery, or radiotherapy initiated after the start of study treatment the reason for its use must be clearly documented.

A whole body bone scan (e.g. Tc-99m bone scan, sodium fluoride PET [NaF-PET] bone scan) can be done to identify location of recurrence in bone tissue. If bone metastases were identified by a bone scan, it has to be confirmed histologically (preferred) or radiographically (by CT, MRI or FDG-PET-CT) if biopsy confirmation is unsafe.

All MRI and CT of the chest should be done with contrast unless contraindicated. If a subject 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 (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 chest should be performed.

MRI or CT of brain with contrast is required at screening. Contrast enhancement should be used for all subsequent imaging unless contraindicated for the subject.

Findings from radiological evaluations (evaluation of suspicion of recurrence or unconfirmed findings) will be recorded in the eCRF.

Table 8-2 Imaging Assessment Collection Plan

Procedure	Screening/Baseline & Pre-operative	During Adjuvant Treatment	Survival follow-up
Chest CT/MRI with contrast or PET-CT* *with diagnostic quality CT; allowed at baseline only	Mandated	Mandated, every 12 weeks (+/- 7 days) for the first year of adjuvant treatment and every 26 weeks thereafter.	Not applicable
Brain MRI/CT	Mandated at screening, if clinically indicated pre-operative	If clinically indicated	Not applicable
Whole body bone scan	If clinically indicated	If clinically indicated (new bone pain or other symptoms of bone metastases)	Not applicable
Unscheduled CT or MRI of involved area, upon any signs or symptoms of recurrence	Not applicable	Upon suspected recurrence	Not applicable

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 may limit or prevent on-site study visits regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

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

Table 8-3 Safety Assessments

Assessment	Specification
Physical examination	A complete physical examination must be performed at screening and later as clinically indicated and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological assessments. A targeted (short) physical exam will be performed as per schedule in Table 8-1 and will include the examination of general appearance and vital signs (blood pressure and pulse). More frequent examinations may be performed at the discretion of the investigator and if medically indicated. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded as an AE.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, respiratory rate, and body temperature. Vital signs will be measured at screening and at subsequent time points as specified in Table 8-1.
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 8-1.
Performance status (PS)	The Eastern Cooperative Oncology Group (ECOG) performance status will be assessed according to the PS scale as specified in Table 8-4 following the schedule given in Table 8-1.

Performance status

Table 8-4 ECOG performance status

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

8.4.1 Laboratory evaluations

The results of the laboratory tests performed locally will be recorded in the eCRF.

Novartis must be provided with a copy of the normal ranges and certification of the all laboratories used to assess participants' safety during study conduct. The investigator is

responsible for reviewing all laboratory reports for participants in the study and evaluating any abnormalities for clinical significance.

At any time during the study up to the safety follow-up visit, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. The severity of laboratory data will be graded using the Common Terminology Criteria for Adverse events (CTCAE) v5.0. (See Section 10.1 for additional information.) Additional analyses are left to the discretion of the investigator.

As per Section 4.6, if participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

Table 8-5 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells (WBC), Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred, percentages are acceptable unless indicated otherwise)
Chemistry	Albumin, ALP, ALT, AST, Gamma-glutamyl-transferase (GGT), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Creatinine Clearance, Direct Bilirubin (only if TBL is ≥ grade 2), TBL, Blood Urea Nitrogen (BUN) or Urea, Amylase, Lipase, fasting Glucose (non-fasting glucose allowed post-baseline) Bicarbonate, Chloride and Uric Acid: at screening and thereafter if clinically indicated.
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If dipstick is abnormal then perform Microscopic Panel (Red Blood Cells, WBC, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or Quick Test (QT), International normalized ratio [INR])
Pregnancy Test	A serum pregnancy test must be performed at screening within ≤ 72 hours before first dose of study treatment, then the schedule of serum and urine pregnancy tests should be performed as indicated in Table 8-1 and Section 8.4.5. If local requirements dictate otherwise, local regulations should be followed.

8.4.1.1 Hematology

Hematology tests are to be performed according to the visit schedule outlined in Table 8-1. For details of the hematology panel refer to Table 8-5. Hematology should be assessed on the actual scheduled day, even if study drug is being withheld.

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

Additional results from unscheduled hematology lab evaluations should be recorded on the appropriate unscheduled visit eCRF.

8.4.1.2 Chemistry

Clinical chemistry tests are to be performed according to the visit schedule outlined in Table 8-1. For details of the biochemistry panel see Table 8-5. Chemistry tests should be assessed on the actual scheduled day, even if study drug 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.

Additional results from unscheduled chemistry lab evaluations should be recorded in eCRF as unscheduled visit.

8.4.1.3 Urinalysis

Dipstick measurements will be performed as per Table 8-5 and according to the schedule of assessments (Table 8-1). Any significant findings on dipstick will be followed up with microscopic evaluation and recorded on the appropriate eCRF page.

8.4.2 Coagulation

Coagulation tests outlined in Table 8-5 will be performed according to the visit schedule outlined in Table 8-1.

8.4.3 Pulmonary Function Tests (PFT)

PFTs must have been performed within 3 months of planned resection and repeated at screening if clinically indicated, and should include lung volumes, spirometry, and diffusion capacity. Abnormal PFTs may be further evaluated with quantitative ventilation/perfusion scanning or cardiopulmonary exercise testing. Additional PFTs should be performed according to the visit schedule outlined in Table 8-1.

Any PFTs already completed during the regular work-up of the subject within 3 months prior to start of treatment, including before signing the main study ICF, can be considered the baseline PFTs for this study.

8.4.4 Electrocardiogram (ECG)

Standard triplicate 12 lead ECG assessments will be performed during screening, pre-dose Cycle 1, day 1, and at end of treatment (see Table 8-1).

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

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.

8.4.5 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 and the definition of post-menopausal, and for a definition of assessment of fertility (males and females), please see Section 5.2. 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 should not donate sperm for the time period specified above.

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 postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

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

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. Additional pregnancy testing might be performed if requested by local requirements.

For women of child-bearing potential, urine pregnancy tests will be required to be performed on day 1 of cycles 1,2,3 and 4 and then every 3 cycles (at each study visit) until the end of treatment with capmatinib. In addition, a serum pregnancy test will be performed at the end of treatment and during the safety follow-up.

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. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

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.

8.4.6 Appropriateness of safety measurements

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

8.5 Additional assessments

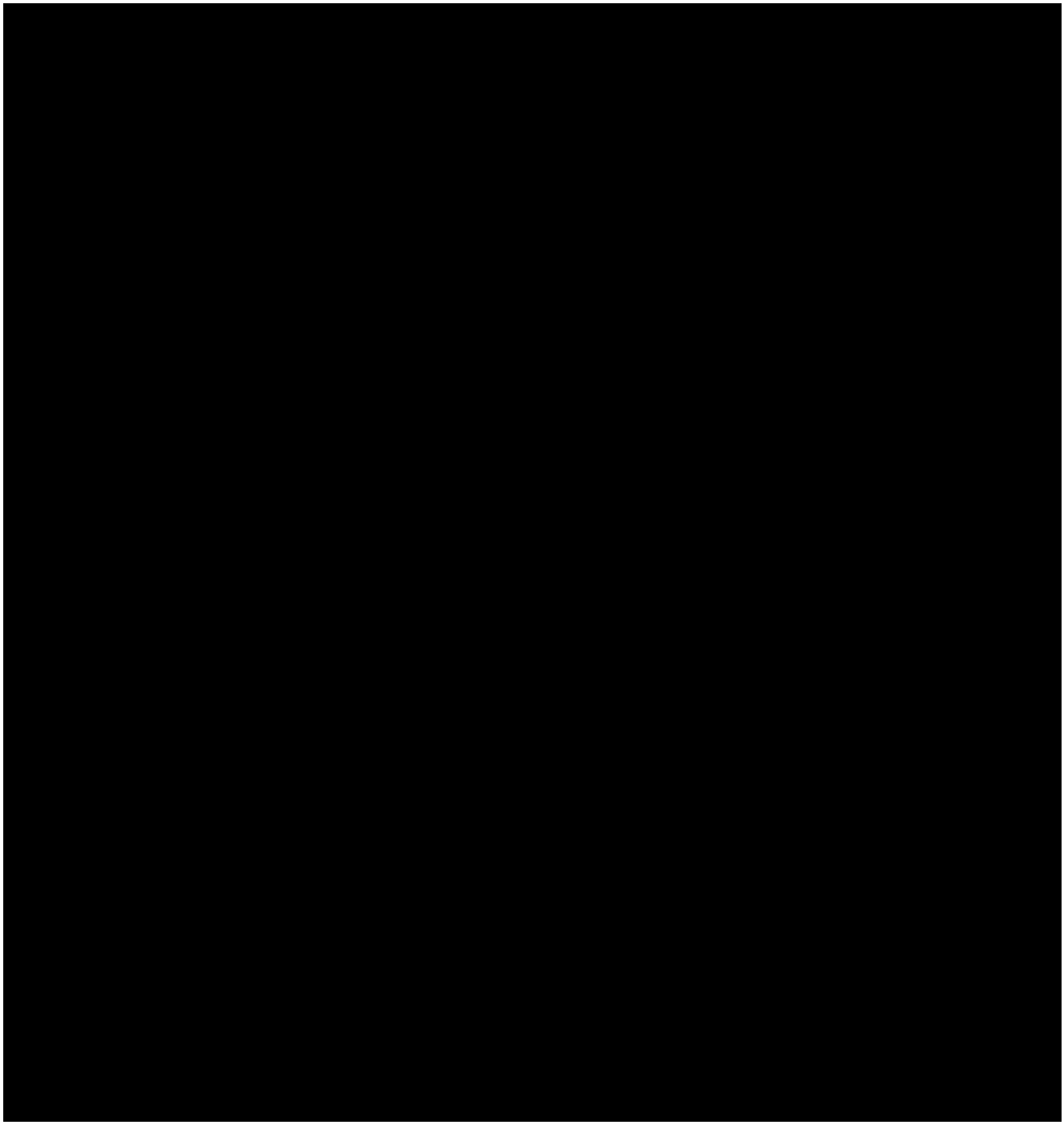
During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible the collection of samples may be modified by Novartis and will be communicated to the Investigator.

8.5.1 Surgery related information

The surgery should be performed as per local guidelines/clinical practice. The following surgery instructions are general recommendations and should only be considered as a guidance.

- Mediastinal lymph node staging by endobronchial ultrasound or mediastinoscopy is encouraged.
- Resection may be accomplished by open or minimally invasive techniques (i.e. clamshell or hemiclamshell incision, robot assisted thoracic surgery, sternotomy, thoracotomy, or video assisted thoracic surgery/thoracoscopy).
- Pathologic complete resection of the primary tumor (R0 resection) should be performed. Anatomic resection by bilobectomy, lobectomy, pneumonectomy, or segmentectomy is strongly preferred. Wedge (nonanatomic) resection can be done for very small (2 cm or less) tumors located peripherally where at least a 1 cm margin in all directions is possible.
- Hilar and mediastinal lymph node dissection or sampling should be performed. For right sided resections, lymph nodes for levels 4R, 7, 10R, and 11R, and for left sided resections lymph nodes from levels 5/6, 7, 10L, and 11L should be dissected or sampled.

Surgery related information, including safety-related, will be collected on the appropriate eCRF page.



8.6 Follow up evaluations

8.6.1 Safety follow up

All subjects will be followed for AEs and SAEs for at least 30 days following the EOT visit. At the end of this period, the investigator should assess and discuss with the subject any AEs observed and concomitant medications taken since discontinuation of study treatment. Subjects whose treatment is permanently discontinued due to an AE (clinical or based on abnormal laboratory value) must be followed until resolution or stabilization of the event, whichever

comes first. In case of an abnormal laboratory value, blood tests should be repeated until resolution or stabilization. See Table 8-1 for list of assessments to be performed at safety follow-up visit.

If a new antineoplastic therapy is initiated after discontinuation of study treatment, only SAEs suspected to be related to study treatment will be collected in the Adverse Events eCRF.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

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

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

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Investigator decision
- Pregnancy (see Section 10.1.4)
- Any situation in which continued study participation might result in a safety risk to the participant
- Disease recurrence
- AE requiring permanent discontinuation of study treatment (see Table 6-3)
- Protocol deviation that results in a significant risk to participant's safety
- Withdraw of consent (see Section 9.1.3)
- Study is terminated by the sponsor (see Section 9.1.5)
- Death
- Lost to follow-up (see Section 9.1.4)

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.3). **Where possible, they should return for the EOT assessments indicated** in Table 8-1 and safety follow-up. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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, in abbreviated visits, the data mentioned in Table 8-1 should be collected at clinic visits or via telephone/email contact.

9.1.2 Discontinuation from study

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

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

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

Participants may voluntarily withdraw consent/oppose to use data/biological samples to participate in the study for any reason at any time. WoC/opposition to use data/biological samples occurs only when a participant:

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

and

- No longer wishes to receive study treatment

and

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

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

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/opposition to use data/biological samples and record this information.

Where consent to the use of personal and coded data is not required, the participant therefore cannot withdraw consent; however, they still retain the right to object to the further collect or use of their personal data.

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

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

All efforts should be made to complete the assessments prior to study discontinuation. If the participant agrees a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the Assessment Table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the ICF. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition

9.1.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed. Participants lost to follow up should be recorded as such on the appropriate eCRF page.

9.1.5 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 from study treatment: Novartis will provide instruction for contacting the participant, when the participant should stop taking drug, when the participant should come in for a final visit(s) that the safety follow up period must be completed and which visits to be performed. 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 participants, study completion is defined as when the subject has completed the 30 day safety follow-up.

Final analysis will be performed when all the participants complete the treatment period or discontinue early, and final CSR will be written.

Participants will continue to receive study treatment until reasons for discontinuation of study treatment are met in Section 9.1.1 or treatment completion. In addition, participants may voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

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):

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

- 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
- Its duration (start and end dates or ongoing) and the outcome must be reported
- Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
- Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
    - Dose not changed
    - Dose Reduced/increased
    - Drug interrupted/permanently discontinued
- Its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal or unknown).

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

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

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

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

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria), 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.

[redacted]

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, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, under no circumstances later than 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

If a new antineoplastic therapy is initiated during the 30-day safety follow-up period, only SAEs suspected to be related to the study treatment will be collected in the AE eCRF.

The following SAE reporting timeframes apply:

- Screen failures (e.g. a participant who is screened but is not treated): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a screen failure must be reported to Novartis.
- Enrolled OR Treated Participants: All SAEs collected between time participant signs ICF until 30 days after the participant has permanently stopped study treatment

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

Any SAEs experienced after the 30 day follow-up period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent from should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up at 1, 3 (for a live birth only) and 12 (for a live birth only) months after the estimated date of delivery to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

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

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate 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 even if not associated with an AE	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 Steering Committee

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

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

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused supplies to Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. 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/delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol

and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/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

It is planned that the data from all centers participating in the study will be combined, so that an adequate number of participants are available for analysis. Novartis and/or a designated CRO will perform all analyses.

All efficacy and safety data will be summarized descriptively for each cohort. Categorical data will be presented in frequencies and percentages. For continuous data, descriptive statistics (mean, standard deviation, median 25th and 75th percentiles, min and max) will be provided. As appropriate, 95% confidence interval will be reported.

Screen failures and the reasons for not starting the study treatment will be reported in a listing, but will not be included in any analysis.

Further details of the statistical analyses including timing and analysis of each endpoints will be fully described 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

12.1.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all enrolled participants to whom study treatment has been assigned and who received at least one dose of any study treatment (i.e. at least one dose of capmatinib administered).

12.1.2 Safety Set

Same definition as of FAS above in Section 12.1.1.

[redacted]

[redacted]

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for all participants enrolled in the study.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term for all participants.

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

12.3 Treatments

The duration of exposure to capmatinib will be presented in days. Dose intensity will be computed as the ratio of actual cumulative dose received and actual duration of exposure. Relative dose intensity will be computed as the ratio of dose intensity and planned dose intensity. The duration of exposure, dose intensity and relative dose intensity will be summarized using descriptive statistics. The duration of exposure will be presented for the cohort. Continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum will be presented.

The number of participants with dose adjustments (reduction, interruption, or permanent discontinuation) and the reasons will be summarized for each cohort. All of the dosing related data will be listed.

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

Categorical data will be summarized as frequencies and percentages.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary objective is to evaluate the major pathologic response (MPR) rate in resection specimens following neoadjuvant capmatinib in the two cohorts (A and B).

Where, Cohort A: Participants with MET exon 14 skipping mutation, irrespective of MET GCN and Cohort B: Participants with High MET amplification.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary efficacy variable is major pathologic response (**MPR**) rate, defined as the proportion of participants with ≤ 10% residual viable cancer cells. MPR rate will be assessed via local review for primary analysis.

[redacted]

12.4.3 Handling of intercurrent events of primary estimand

The intercurrent events of interest are:

- The treatment **discontinuation** for any reason: Tumor assessment data collected irrespectively of treatment discontinuation until start of antineoplastic therapy will be included to derive MPR (composite strategy)
- Start of any **other antineoplastic therapy**: If any other antineoplastic therapy or other procedures are undertaken, any subsequent assessment will be excluded from the MPR assessment (hypothetical strategy)
- Any public health emergency as declared by local or regional authorities i.e. **pandemic,** epidemic or natural disaster (treatment policy strategy)

As appropriate, in order to evaluate the impact of these identified intercurrent events sensitivity analyses of the primary efficacy endpoint will be performed with and without those intercurrent events. Number and percentages of the summary measure, the major pathologic response (MPR), and its exact 95% confidence interval (CI) will be provided by cohort.

As the study is being initiated and will be ongoing during COVID 19 pandemic, in order to address the impact order to address the impact of COVID-19 (if any) on discontinuation, protocol deviations, disease status, rescue medications, dose interruptions, AEs and labs assessments and on missing data will be explored.

Detail will be discussed in the Statistical Analysis Plan (SAP).

12.4.4 Handling of missing values/censoring/discontinuation

Only participants with non-missing MPR will be considered for the evaluation of MPR following neoadjuvant capmatinib therapy. MPR achieved prior to any additional anticancer therapy will be considered as responses in the calculation of the MPR irrespective of the number of missed assessments before response.

Participants with a MPR of 'Unknown' will be considered as non-responders when estimating MPR.

Participants with no available data will be considered as non-responders when estimating MPR.

12.4.5 No imputation will be performed for the missing data. Sensitivity and Supportive analyses for primary endpoint/estimand(s)

As part of supportive analysis, the following subgroup analyses for the primary efficacy variable will be performed to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics:

- Gender (male vs. female)
- Age (<65 vs. ≥65 years)
- ECOG performance status (0 vs. 1)
- Nodal stage (N0 vs. N1 vs. N2)

Number and percentage of patients receiving: no adjuvant therapy, standard of care chemotherapy alone, and SOC chemotherapy + adjuvant therapy will also be summarized

As appropriate, a sensitivity analysis will be performed on the primary efficacy evaluating the impact of the above intercurrent events, if any.

Further details will be provided in the SAP.

12.5 Analysis of secondary endpoints

The secondary objectives for the study are to evaluate complete pathologic response (pCR) rate following neoadjuvant capmatinib therapy, overall response rate (ORR) and safety and tolerability for each cohort.

12.5.1 Secondary Efficacy endpoint(s)

The secondary efficacy endpoints will be assessed using the Full Analysis Set (FAS). The following analyses will be performed for each cohort:

Complete Pathologic response (pCR) rate is defined as the as the proportion of participants with no residual viable cancer cells. pCR rate will be assessed via both central and local review. pCR rate will be summarized using binomial response rate and its 95% confidence interval will be presented for each cohort following neoadjuvant capmatinib therapy using Coppler-Pearson method.

Overall response rate (ORR) is defined as the proportion of participants with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST v 1.1. ORR will be calculated using local investigator review.

ORR will be summarized using binomial response rate and its 95% confidence interval will be presented each cohort using Coppler-Pearson method.

Disease Free Survival (DFS) **is** defined as the time from date of end of adjuvant therapy with capmatinib to the date of event defined as the recurrence of cancer or death due to any cause. Disease free survival will be presented at 24, 36 and 60 months after adjuvant capmatinib treatment for each cohort. The disease free survival distribution will be estimated using the Kaplan-Meier method, and the estimates of the 25th, median and 75th percentile of the DFS and 95% confidence intervals will also be presented.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used and data will be presented for each cohort. Listings and tables will also be presented by each cohort for all participants.

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

1. Pre-treatment period: from the day of subject's informed consent to the day before first dose of study medication.

2. On-treatment period: from day of first dose of study medication to 30 days after the date of last actual administration of any study medication.

3. Post-treatment period: starting at day 31 after last dose of study medication.

If dates are incomplete in a way that clear assignment to pre-, on-, or post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period. Additional details to address incomplete AE and/or dosing dates will be addressed in the SAP.

Additional summaries will be displayed to report deaths, all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 30 days after last administration of any study treatment.

Adverse events

Summary tables for AEs will include only AEs that started or worsened during on-treatment periods, the treatment-emergent AEs and will be presented for each cohort.

The incidence of treatment-emergent AEs will be summarized by system organ class and preferred term, severity (based on CTCAE v 5.0 grades), types of adverse event, and relation to study treatment.

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

All reported 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 starting during the pre-treatment and post-treatment period will be flagged.

Vital signs

Data on vital signs will be tabulated and listed for each cohort, notable values will be flagged.

12-lead ECG

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

Categorical analysis of QT/QTc interval data based on number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented for each cohort. In addition, a listing of these participants will be produced. All ECG data will be listed by subject and visit/time, abnormalities will be flagged.

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE v 5.0 grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE v 5.0 grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be applicable.

For laboratory tests where grades are not defined by CTCAE v 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

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

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

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

- Worse post-baseline CTCAE v 5.0 grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v 5.0 grades to compare baseline to the worst on-treatment value.

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

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

Other safety evaluations

Tolerability

Tolerability of study drug treatment will be assessed by summarizing the number of treatments dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by subject and summarized for each cohort.

[redacted]

[redacted]

12.7 Interim analyses

As appropriate, annual interim analyses will be planned for publication or any regulatory purpose.

An interim analysis will be performed for both the cohorts after Stage 1 of the study to make a determination to go or not to the Stage 2 based on pre-specified efficacy threshold. Efficacy and safety data with the Stage 1 participants will be analyzed. Final analysis will be performed when all the participants complete the treatment period or discontinue early, and CSR will be written.

[redacted]

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the 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

The following 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.

- Thank You letter

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including

incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

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

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: List of concomitant medications for participants on capmatinib

Table 16-1 Medications that require caution when concomitantly used with capmatinib

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

Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (drug-interactions.medicine.iu.edu/Main-Table.aspx), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies". This list may not be exhaustive and could be updated periodically. Please refer to the above mentioned database for the latest information. NTI: narrow therapeutic index

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

Table 16-2 Capmatinib: prohibited drugs

Mechanism of Interaction	Drug Name (generic)
Strong CYP3A4 inducer	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (Hypericum perforatum)

Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (drug-interactions.medicine.iu.edu/Main-Table.aspx), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies". This list may not be exhaustive and could be updated periodically. Please refer to the above mentioned databases for the latest information.

16.2 Appendix 2: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

Document type:	TA Specific Guideline
Document status:	Version 3.2: February 11, 2016 Version 3.1: November 29, 2011 Version 3: October 19, 2009 Version 2: January 18, 2007 Version 1: December 13, 2002
Release date:	11-Feb-2016

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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

16.2.1 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 16.2.2 and the definition of best response in Section 16.2.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.2.3.2 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 16.2.4 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.

16.2.2 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).

16.2.2.1 Definitions

16.2.2.1.1 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 participants without measurable disease see Section 16.2.3.2.9.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥ 15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥ 10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

16.2.2.1.2 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 participants be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how participants with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.2.3.2.9.

16.2.2.2 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of participants, 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.

16.2.2.3 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 16.2.2.1.1.
- **Nodal target**: See Section 16.2.2.1.1.

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.

16.2.2.4 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 16-3) and non-target lesions (Table 16-4) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-5) as well as the presence or absence of new lesions.

16.2.2.4.1 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.

16.2.2.4.2 Determination of target lesion response

Table 16-3 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions

Response Criteria	Evaluation of target lesions
	recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm [2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1.] SOD for CR may not be zero when nodal lesions are part of target lesions
[2.] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3.] In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.2.2.2)

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 16-3 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to participants who have not achieved target response of CR. For participants who have achieved CR, please refer to last bullet in this section.
- For those participants who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement

recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.

- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria

16.2.2.4.3 Determination of non-target lesion response

Table 16-4 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline[2].

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

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned
- The response for non-target lesions is**CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK)
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 16.2.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.2.2.4.4 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 16.2.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ³ 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 16.2.2.2.

16.2.2.5 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 16-5.

Table 16-5 Overall lesion response at each assessment

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

[1.] This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2.] Once confirmed PR was achieved, all these assessments are considered PR.
[3.] As defined in Section 16.2.2.4.

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.

16.2.3 Efficacy definitions

The following definitions primarily relate to participants who have measurable disease at baseline. Section 16.2.3.2.8 outlines the special considerations that need to be given to participants with no measurable disease at baseline in order to apply the same concepts.

16.2.3.1 Best overall response

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

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

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

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD)

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

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

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

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (³30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ³20% 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 participants' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of participants 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 participants with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize participants 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 participants 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 participants with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all participants 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. Participants 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, participants 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).

16.2.3.2 Time to event variables

16.2.3.2.1 Progression-free survival

Usually in all Oncology studies, participants 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.

[redacted]

16.2.3.2.3 Time to progression

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

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

16.2.3.2.4 PFS2

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

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

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

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

16.2.3.2.5 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure

may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

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

16.2.3.2.6 Duration of response

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

It is recommended that an analysis of all participants (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 participants (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 participants throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For participants 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 participants 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 participants 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.

16.2.3.2.7 Time to response

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

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 16.2.3.2.6. It is recommended that an analysis of all participants (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 participants should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all participants, participants who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for participants 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 participants 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.

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

Assessment date

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

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

Start Dates

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

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

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 16.2.3.2.8).

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

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

16.2.3.2.9 Handling of participants with non-measurable disease only 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. 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 participants 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 participants with measurable disease at baseline, participants without measurable disease should also be incorporated in an appropriate manner. The overall response for participants with non-measurable disease is derived slightly differently according to Table 16-6.

Table 16-6 Overall lesion response at each assessment: participants 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 16.2.2.4.

In general, the **non-CR/non-PD response** for these participants is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response participants 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 participants 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 participants with only non-measurable disease at baseline, handling participants with a best response of CR as "responders" with respect to ORR and all other participants as "non-responders".

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

16.2.3.2.10 Sensitivity analyses

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

Based on definitions outlined in Section 16.2.3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 16-7 Options for event dates used in PFS, TTP, duration of response

Situation		**Options for end-date (progression or censoring)[1]** **(1) = default unless specified differently in the protocol or RAP**	**Outcome**
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy	As per above situations Censored Censored Event

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
		(3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1.] =Definitions can be found in Section 16.2.3.2.7.
[2.] =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.2.3.2.7.
[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 participants 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.

16.2.4 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).

16.2.4.1 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).

16.2.4.2 End of treatment phase completion

Participants **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 participants 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.

Participants 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.

16.2.4.3 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.

Participants 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

16.2.4.4 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 participants with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

16.2.4.5 Programming rules

The following should be used for programming of efficacy results:

16.2.4.5.1 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.

16.2.4.5.2 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 16.2.3.2.7). 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.

16.2.4.5.3 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.

16.2.4.5.4 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)'.

16.2.4.5.5 Study/project specific programming

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

16.2.4.5.6 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 16-7)
- 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 16.2.3.2.7. 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 participants 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.