NOVARTIS

Novartis Research and Development

INC280/Capmatinib

Clinical Trial Protocol CINC280I12201 / NCT04139317

A randomized, open label, multicenter phase II study evaluating the efficacy and safety of capmatinib (INC280) plus pembrolizumab versus pembrolizumab alone as first line treatment for locally advanced or metastatic non-small cell lung cancer with PD-L1≥ 50%

Document type:	Amended Protocol Version
EUDRACT number:	2019-002660-27
Version number:	v03 (Clean)
Clinical trial phase:	II
Release date:	21-Apr-2021

Table of contents

List of tables

List of figures

List of abbreviations

Ab	Antibody
ADA	Antidrug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BCRP	breast cancer resistance protein
b.i.d.or BID	bis in die/twice a day/ twice daily
BMI	Body mass index
BUN	Blood urea nitrogen
CNS	Central nervous system
CR	Complete response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography
CTC	Common Terminology Criteria
CTT	Clinical Trial Team
CV	coefficient of variation
DBP	Diastolic blood pressure
DCR	Disease control rate
DDI	Drug-drug interactions
DILI	Drug-induced liver injury
DLCO	Diffusing capacity corrected for hemoglobin
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOT	End of treatment
eSAE	Electronic serious adverse event
ESMO	the European Society for Medical Oncology
eSource	Electronic source
FAS	Full analysis set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose

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
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HGF	Hepatocyte growth factor
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
IUD	Intrauterine device
IUS	Intrauterine system
IEC	Independent Ethics Committee
IG	Immunogenicity
ILD	Interstitial lung disease
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
i.v.	intravenous
LDH	lactate dehydrogenase
LFTs	Liver function tests
LLN	lower limit of normal
LLOQ	lower limit of quantification
mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic(s)
PET	Positron emission tomography
PFS	Progression-free survival
[redacted]	[redacted]
PFT	Pulmonary function tests
PK	Pharmacokinetic(s)

p.o.	oral(ly)
PPS	Per-Protocol Set
PR	Partial response
PT	prothrombin time
PTT	Partial Thromboplastin Time
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase two dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SC	Steering Committee
SD	standard deviation or stable disease
SmPC	Summary of Product Characteristics
SpO2	Oxygen saturation
TKI	Tyrosine kinase inhibitor
TMB	Tumor Mutational Burden
TPS	Tumor proportion score
TSH	Thyroid Stimulation Hormone
TTR	Time-to-response
ULN	upper limit of normal
VATS	Video-assisted thoracic surgery
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 subject
Cohort	A specific group of subjects 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 subject 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 subject or at a later point in time as defined by the protocol
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
Investigational drug	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
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 subjects with established disease and in those with newly-diagnosed disease
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject 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
Randomization number	A unique identifier assigned to each randomized subject

Screen Failure	A subject 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 (Electronic Source)
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 subject
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures
Study treatment discontinuation	When the subject 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
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm	A treatment arm defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 3 (21-Apr-2021)

Amendment rationale

The main purpose of this amendment is to modify the study conduct and data analysis following the enrollment halt on 21-Jan-2021 due to lack of tolerability observed in the capmatinib plus pembrolizumab arm. The decision to halt enrollment, supported by the Data Monitoring Committee (DMC), was made based on the observation that subjects who receive capmatinib plus pembrolizumab combination treatment had higher rates of SAEs/AEs, leading to dose interruption and/or discontinuation of both study treatments compared to subjects in the pembrolizumab single agent arm.

Immediately following the enrollment halt, below procedural changes have been performed:

- Capmatinib treatment was discontinued in subjects on the combination arm. All ongoing subjects continue to receive single-agent pembrolizumab, a registered and commercialized treatment for the study indication.
- Randomization information was released to the clinical trial team.
- Termination of capmatinib PK sample collection, effective 21-Jan-2021
- [redacted]
- Termination of pembrolizumab PK/IG sample collection as per memorandum dated 04-Feb-2021

This protocol amendment incorporates significant changes as follow:

- To simplify the study procedures,
  - As pembrolizumab is a registered and commercialized treatment for the study indication, the efficacy and safety assessments will be performed as per each institution's standard of care. The efficacy and safety assessment results (except reporting of adverse events, see next bullet point) will no longer be captured in the eCRF. Centralized collection of imaging data will not be performed.
  - The reporting of adverse events, including serious adverse events, and associated concomitant medication will remain to be captured in the eCRF until 30 days following the last administration of study treatment.
- To refine the definition of end of study as the earliest occurrence of one of the following:
  - discontinued study treatment and completed the safety FU or
  - died or
  - withdrawn consent or
  - been lost to follow-up.
- To allow earlier disbandment of DMC, as an independent review of safety and efficacy data will not be required after the release of randomization information to the study team.

- To cancel the originally planned administrative interim analysis when approximately 30 PFS events have been observed and the primary analysis when 50 PFS events have been observed, and adjust the planned data analysis and statistical methods:
  - The analysis of primary efficacy endpoints will now be based on Kaplan-Meier analysis of PFS of the two treatment arms. Halting of further enrolment, discontinuation of capmatinib in subjects on the combination arm and the stopping of efficacy data collection as of this amendment would make the previously planned Bayesian PFS analyses uninterpretable.
  - The definition of PFS endpoint is updated to consider censoring of subjects before the start of a subsequent anti-neoplastic therapy, as it is considered more appropriate for NSCLC patients.
  - For subjects on the combination arm, PFS and BOR will also be censored before the date of sponsor's decision to discontinue capmatinib, as hereafter the treatment will be switched to pembrolizumab alone. In addition, to explore the potential lasting effect of capmatinib, supportive analyses on PFS and BOR will also be performed based on all available tumor assessments irrespective of sponsor's decision to discontinue capmatinib.

This protocol amendment will also incorporate the following changes:

- To allow flexibility when conducting palliative radiotherapy during the study, radiotherapy with palliative intent, including but not limited to analgesic purposes or for lytic lesions at risk of fracture, may be carried out if required.
- To align pembrolizumab handling and treatment with the drug's approved label,
  - The recommended treatment modifications and follow up for toxicities will refer to locally approved label for pembrolizumab.
  - Treatment beyond disease progression with pembrolizumab will not be allowed as part of this study.
- Since all ongoing subjects continue to receive single-agent pembrolizumab, a registered and commercialized treatment for the study indication, subjects are allowed to be transitioned to commercial pembrolizumab and discontinued from the study.
- Single-agent pembrolizumab is a well-established standard treatment for the study indication, therefore disease progression follow-up and survival follow-up will not be performed. Information on antineoplastic therapies after study treatment discontinuation will not be collected.
- The assessment of benefit/risk concluded the absence of additional risks related to COVID-19. To ensure subject safety and trial integrity during a public health emergency, mitigation procedures are added in the relevant sections.

Other minor changes and corrections are made throughout the protocol for consistency and/or clarification.

Study update

As of 21-Jan-2021 when enrollment was halted, 76 out of the targeted 96 subjects had been randomized, including 51 subjects in capmatinib plus pembrolizumab arm and 25 subjects in pembrolizumab alone arm. As of 15-Mar-2021, 50 subjects are ongoing in this trial with single-agent pembrolizumab treatment.

Changes to the protocol

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

- Protocol Summary: updated Population, Study treatment and Data analysis
- Section 3: added a footnote to indicate capmatinib treatment discontinuation
- Section 4.4: added that the planned administrative interim analysis will not be performed
- Section 4.5: added the assessment for pembrolizumab single agent treatment
- Section 4.6: added this new section Rationale for public health emergency mitigation procedures
- Section 6.1: added conditions for pembrolizumab treatment continuation and discontinuation
- Section 6.1.4.1: added that treatment beyond disease progression will no longer be allowed
- Section 6.2.1.1: updated the condition when radiotherapy is allowed
- Section 6.4: added that randomization information was released to CTT after enrollment halt
- Section 6.5.1: added that recommended treatment modifications for pembrolizumab should refer to the locally approved label and removed former Table 6-5
- Section 6.5.2: added that toxicity follow-up should refer to the locally approved label of pembrolizumab
- Section 7 and Section 8: added mitigation procedures under public health emergency
- Section 8: added Table 8-2b for updated assessment schedule
- Section 8.2: added the purpose of collecting subject race and ethnicity information
- Section 8.3 and Section 8.4: added that efficacy and safety assessments will be performed as per each institution's standard of care, and that imaging data will no longer be centrally collected
- Section 8.5.1 and Section 8.5.2: added that PK/IG [redacted] sample collection has been terminated
- Section 9.1.1: updated the condition for discontinuation of study treatment, and the procedures after treatment discontinuation
- Section 9.2.1: updated the definition of end of study
- Section 9.2.2.1: added that antineoplastic therapies since discontinuation of study treatment will not be collected
- Section 9.2.2.2 and Section 9.2.2.3: added that disease progression follow-up and survival follow-up will not be performed

- Section 10.2.1: added that DMC will be disbanded since randomization information has been released to CTT
- Section 12: removed the primary analysis planned to be performed prior to the final CSR, and clarified the analysis of all primary and secondary endpoints will be performed after the end of the study
- Section 12.1.2: removed the definition of Per-Protocol Set (PPS) since no supportive analysis based on PPS will be performed
- Section 12.4.1: removed the statement of primary objectives and updated the primary endpoint estimation.
- Section 12.4.1.2: updated the statistical analysis method to be used for the primary analysis of the primary endpoint PFS
- Section 12.4.1.3: changed the definitions of primary analyses of PFS regarding the censoring of the patient before the start of a subsequent anti-neoplastic therapy or the discontinuation of capmatinib due to sponsor's decision
- Section 12.4.1.4: updated the supportive analyses for the primary endpoint
- Section 12.5: updated the secondary efficacy endpoint estimation
- Section 12.5.1: added the censoring rules for the definitions of BOR, TTR and DOR.
- Section 12.5.3: updated the PK parameters for capmatinib and pembrolizumab
- Section 12.7: removed the planned administrative interim analysis

IRBs/IECs

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

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

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

Amendment 2 (17-Feb-2020)

Amendment rationale

The main purpose of this amendment is to address Health Authorities' requests as listed below:

- To add background clinical pharmacology information for capmatinib
- To exclude patients with active infection or history of allogeneic tissue/organ transplantation and to provide the recommended treatment modifications for pembrolizumab in details, in order to align with the EU Summary of Product Characteristics (SmPC) for pembrolizumab
- To interrupt capmatinib treatment in case of hypersensitivity reactions, as SAEs of hypersensitivity have been reported as suspected to be related to study treatment in the capmatinib IB
- To clarify that SAE reporting is required for any progression of malignancy suspected to be related to study treatment and meeting the SAE definition
- To conduct a safety review by DMC after the first 6 randomized patients have been followed up for at least 6 weeks from randomization or have discontinued earlier

In addition, after a recent occurrence of a case of myocarditis, the dose modification guidelines for protocols using capmatinib in combination with PD-1 inhibitors have been updated to mandate permanent discontinuation of study treatment in case of myocarditis grade ≥2 or other cardiac event grade ≥3. The recommended clinical management guidelines in case of such an event have also been provided.

Also, to align with clinical practice, if a patient's HCV antibody (Ab) test is negative, then further HCV RNA testing is not required.

Other minor changes and corrections were made throughout the protocol for consistency and/or clarification.

Study update

As of 22-Jan-2020, one patient is being screened and no subject has been treated in this trial.

Changes to the protocol

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

- Section 1.1.1: added background clinical pharmacology information for capmatinib
- Section 5.2: excluded patients with active infection or history of allogeneic tissue/organ transplantation
- Section 6.2.1.1: removed "while taking capmatinib" to clarify that the permitted concomitant medications apply to all subjects
- Section 6.5.1:
  - added recommendation in case the causality of toxicity cannot be clearly attributed
  - added Table 6-5 Recommended treatment modifications for pembrolizumab

- Table 6-7:
  - clarified definition of grade 3 and 4 febrile neutropenia as per CTCAE v5.0
  - added dose modifications for capmatinib in case of myocarditis or other cardiac event
  - added dose modifications for capmatinib in case of hypersensitivity reaction
- Section 7: listed the informed consents included in this study
- Section 8.3.1: corrected the baseline imaging assessment period from prior to "the first dose of study treatment" to prior to "randomization"
- Table 8-6: specified HBcAb should test for IgG, added HCV Ab as a hepatitis marker, and clarified when HBV DNA and HCV RNA tests are not required.
- Section 10.1.1: clarified progression of malignancy must be reported as an SAE if the investigator considers it is related to study treatment and meets the SAE definition
- Section 10.2.1: added a safety review by DMC after the first 6 randomized patients have been followed up for at least 6 weeks from randomization or have discontinued earlier
- Section 12.7: clarified that development decisions will be made by a Novartis Committee based on interim analysis results

IRBs/IECs

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

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

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

Amendment 1 (05-Nov-2019)

Amendment rationale

The main purpose of this amendment is to address Health Authorities' requests to provide specific recommendations of concomitant medications to treat diarrhea and nausea toxicities.

In addition, free T3 testing was removed from thyroid function monitoring, and total T3 will be tested if abnormal thyroid function is suspected. This change is made to be in line with standard clinical practice.

Unintended references to central ECG monitoring for cardiac toxicity follow up were removed to reflect the study conduct.

Other minor changes and corrections were made throughout the protocol for consistency and/or clarification.

Study update

As of 05-Nov-2019, no subjects have been screened or treated in this trial.

Changes to the protocol

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

- Table 6-7: The descriptions of central ECG were removed. Follow-up evaluations for toxicities "Diarrhea" and "Nausea and Vomiting" were updated.
- Table 8-2, 8-6: Modified the thyroid panel.
- Section 15 References: A newly cited reference was added.

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.

Protocol summary

Protocol number	CINC280I12201
Full Title	A randomized, open-label, multicenter phase II study evaluating the efficacy and safety of capmatinib (INC280) plus pembrolizumab versus pembrolizumab alone as first line treatment for locally advanced or metastatic non-small cell lung cancer with PD-L1≥ 50%
Brief title	Study of efficacy and safety of capmatinib in combination with pembrolizumab versus pembrolizumab alone in subjects with non-small cell lung cancer with PD-L1≥ 50%
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose is to evaluate the efficacy and safety of the combination of capmatinib with pembrolizumab compared to pembrolizumab alone as first-line treatment for subjects with locally advanced or metastatic NSCLC who have PD-L1 expression ≥ 50% and have no EGFR mutation or ALK rearrangement. Capmatinib has demonstrated immunomodulatory activities when combined with an anti-PD1 antibody in preclinical tumor models irrespective of MET dysregulation. The combination of capmatinib with checkpoint inhibitors has been established to be tolerable and could provide additional clinical benefit to the subjects.
Primary Objective(s)	To evaluate the efficacy of capmatinib plus pembrolizumab in comparison to pembrolizumab alone by assessing progression-free survival (PFS) based on local investigator assessment per RECIST 1.1.
Secondary Objectives	Objective 1: To evaluate the anti-tumor activity of capmatinib plus pembrolizumab in comparison to pembrolizumab alone, by assessing Objective response rate (ORR), disease control rate (DCR), time-to-response (TTR) and duration of response (DOR) based on local investigator assessment as per RECIST 1.1 and overall survival (OS). Objective 2: To characterize the safety profile of capmatinib plus pembrolizumab and pembrolizumab alone, by assessing the incidence and severity of AEs and SAEs, AEs leading to dose interruption, dose reduction and dose discontinuation. Objective 3: To characterize the pharmacokinetics (PK) of capmatinib and pembrolizumab by measuring the PK parameters and concentration. Objective 4: To evaluate the prevalence and incidence of immunogenicity of pembrolizumab by assessing the antidrug antibodies (ADA) prevalence at baseline and ADA incidence on treatment of pembrolizumab.
Study design	This is a randomized, open-label, multicenter, phase II study evaluating the efficacy and safety of capmatinib plus pembrolizumab in comparison to pembrolizumab alone. Subjects in both treatment arms will receive up to 35 cycles (~24 months) of study treatment.

Population	The study will include male or female adult subjects diagnosed with advanced or metastatic, squamous or non-squamous non-small cell lung cancer (NSCLC), without EGFR or ALK alteration and with PD-L1 high expression (TPS≥ 50%) with no prior treatment for their metastatic or advanced disease. Approximately 96 subjects will be randomized including 64 subjects in capmatinib plus pembrolizumab arm and 32 subjects in pembrolizumab alone arm. The study enrollment has been halted since 21-Jan-2021, when 76 subjects had been randomized, including 51 subjects in capmatinib plus pembrolizumab arm and 25 subjects in pembrolizumab alone arm.
Key Inclusion criteria	• Histologically confirmed and documented locally advanced stage III or stage IV NSCLC (per AJCC/IASLC v.8) for treatment in the first-line setting. Treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy (other than immunotherapies) is allowed as long as therapy was completed at least 6 months prior to the diagnosis of advanced or metastatic disease. • Both EGFR wild type status and ALK-negative rearrangement (tumor with BRAF V600 mutation or ROS-1 rearrangement will be excluded, if required by local guidelines) • High PD-L1 expression (TPS ≥ 50%). • At least one lesion evaluable by RECIST 1.1 • ECOG performance status ≤ 1 • Have adequate organ function
Key Exclusion criteria	• Prior treatment with a MET inhibitor or HGF-targeting therapy • Prior immunotherapy (e.g. anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways). • Have known hypersensitivity to any of the excipients of capmatinib (crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes) or monoclonal antibodies. • Have untreated symptomatic central nervous system (CNS) metastases. • Have received or will receive a live vaccination within 4 weeks prior to first dose of study treatment. • Active hepatitis B or C
Study treatment	• Capmatinib (INC280) plus pembrolizumab • Pembrolizumab alone Following the study enrollment halt, capmatinib treatment has been discontinued in all subjects. Ongoing subjects are treated with pembrolizumab alone.
Efficacy assessments	• Tumor response assessment per RECIST 1.1 • Survival assessment
Pharmacokinetic assessments	• Concentration and pharmacokinetic (PK) parameters • Pembrolizumab Immunogenicity (IG)

Key safety assessments	• Monitoring of laboratory assessments in blood and urine • Adverse event monitoring • Pregnancy tests in blood and urine
Other assessments	[redacted]
Data analysis	The analysis of primary efficacy endpoints will be based on Kaplan-Meier curves for PFS as well as estimated median PFS along with their two-sided 95% confidence intervals for each treatment arm. The full analysis set (FAS) will be used. The secondary endpoints (overall response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DOR) and overall survival (OS) will be analyzed based on FAS and presented by treatment arms. Aggregated safety data analysis will be performed and reviewed by the Data monitoring committee (DMC) on a regular basis. The first review will occur after the first 6 randomized patients have been followed up for at least 6 weeks from randomization or have discontinued earlier. The second review will occur after the first 12 randomized patients have been followed up for at least 6 weeks from randomization or have discontinued earlier. Subsequent reviews on safety data will be conducted every 6 months. Following the enrollment halt, the randomization information was released for internal data review and to address Health Authorities' queries. As a result, independent data review will not be performed and DMC will be disbanded.
Key words	INC280, capmatinib, pembrolizumab, NSCLC, PD-L1, EGFR wild type, ALK, MET inhibitor, squamous, non-squamous

1 Introduction

1.1 Background

Lung cancer is the leading cause of cancer death. In 2012, an estimated 1.8 million people were diagnosed with lung cancer globally, resulting in 1.6 million deaths (Ferlay et al 2015). In 2019, an estimated 228,150 new cases (116,440 in men and 111,710 in women) will be diagnosed in the United States, and 142,670 deaths are estimated because of the disease (Siegel et al 2019). Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) are the two main types of lung cancer, accounting for 80-85% and 10-15% of cases respectively. The majority (70%) of NSCLC patients present with advanced disease (Molina et al 2008). Only 25-30% of subjects present with surgically resectable disease, and only half of them are disease-free at 5 years (Molina et al 2008, Maeda et al 2010, American Community Survey 2012). For early-stage NSCLC (stage I, selected node negative IIA), surgery is the treatment of choice. For patients with locally advanced NSCLC (inoperable stage II (node positive) and stage III disease), concurrent chemoradiation is the recommended treatment. (O'Rourke et al 2010, Curran et al 2011, Sause et al 2000). Patients with advanced/metastatic NSCLC without targetable oncogenic drivers are usually treated with chemotherapy and immunotherapy. Patients with targetable alterations (such as sensitizing EGFR mutations, ALK rearrangement, BRAF V600E mutation, ROS-1 rearrangement, and NTRK gene fusion) are treated with targeted treatments (NCCN v15 2019).

The median overall survival of metastatic NSCLC patients treated with platinum–based doublet chemotherapy as first-line chemotherapy is 11-14 months (Gandhi et al 2018, Paz-Ares et al 2018, Mok et al 2019). Maintenance therapy with pemetrexed is used in non-squamous NSCLC treatment to prolong response to therapy for responding patients or those whose disease is stable after first-line therapy. (Alimta®USPI 2004) (Alimta®SmPC 2009).

Immunotherapy has further shaped the treatment landscape of advanced NSCLC patients, both in the pretreated and treatment-naive setting. Monoclonal antibodies that block the interactions between PD-1 and immune suppressing ligands, PD-L1 and PD-L2 (nivolumab, durvalumab, pembrolizumab, and atezolizumab) have demonstrated significant activity as monotherapy and superiority over single agent chemotherapy in pretreated NSCLC (Novello et al 2016, Langer et al 2016, Antonia et al 2018).

Durvalumab has been approved as consolidation therapy for patients with unresectable stage III NSCLC patients whose disease has not progressed following concurrent chemoradiation (Antonia et al 2018).

Pembrolizumab has been approved as a single agent in the first-line treatment of PD-L1 expressing, locally advanced and metastatic NSCLC. The approval was based on the results of KEYNOTE-042 study (Mok et al 2019), a randomized, open-label, controlled, phase 3 study, comparing pembrolizumab with chemotherapy for previously untreated, PD-L1 $\geq$ 1%, locally advanced or metastatic NSCLC, which do not harbor EGFR or ALK aberrations. Survival benefit of pembrolizumab monotherapy over chemotherapy is seen in this study (mOS 16.7 vs 12.1 months), but the result was largely driven by patients with high PD-L1 expression (TPS $\geq$ 50%) (mOS 20.0 vs 12.2 months). KEYNOTE-024, a randomized, open label, phase 3 study, comparing pembrolizumab to platinum-based chemotherapies in previously untreated, stage IV NSCLC, with high PD-L1 expression, demonstrated that a high level of PD-L1

expression (TPS ≥ 50%) predicts response to pembrolizumab (Reck et al 2016). Approximately 30% of advanced NSCLC patients have PD-L1 high expression tumor (TPS ≥ 50%). Pembrolizumab has also been approved in combination with pemetrexed and platinum-doublet chemotherapy as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations (Gandhi et al 2018), and in combination with carboplatin and either paclitaxel or albumin-bound paclitaxel as first-line treatment of patients with metastatic squamous NSCLC (Paz-Ares et al 2018).

Nivolumab has been approved for patients who have previously received chemotherapy for both squamous and non-squamous lung cancer on the basis of two randomized phase III trials (Borghaei et al 2015, Brahmer et al 2015) that demonstrated superior OS for nivolumab over docetaxel in both squamous and non-squamous NSCLC. In the first-line setting, nivolumab was not superior to platinum-based doublet chemotherapy in patients with PD-L1 ≥ 1% based on CheckMate-026 study (Carbone et al 2017). A second study, CheckMate-227, demonstrated Progression Free Survival (PFS) improvement of the combination of nivolumab and ipilimumab over chemotherapy in patients with high tumor mutational burden NSCLC (regardless of PD-L1 levels) (Hellmann et al 2018).

Atezolizumab has been approved for previously treated NSCLC with progression on or following a platinum-containing regimen based on superior OS over docetaxel chemotherapy (Rittmeyer et al 2017) regardless of the PD-L1 expression and of the histology. In first-line treatment for non-squamous advanced NSCLC patients, atezolizumab in combination with bevacizumab plus platinum-based chemotherapy demonstrated PFS benefit over bevacizumab plus chemotherapy (Socinski et al 2018) with an improvement in OS (Socinski et al 2018) regardless of PD-L1 expression and EGFR or ALK genetic aberration. Additionally, these studies did not demonstrate any significant OS or PFS benefit in this setting between the additions of either atezolizumab or bevacizumab to a platinum-based chemotherapy. In first-line treatment of squamous NSCLC the addition of atezolizumab to carboplatin plus nab-paclitaxel in a phase III trial, IMpower 131, demonstrated a PFS benefit and the OS data is still awaited (Jotte et al 2018).

1.1.1 MET and capmatinib (INC280)

In human malignant disease, 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 (Christensen et al 2005). Capmatinib is a small adenosine triphosphate (ATP) competitive, orally bioavailable, highly potent, and selective reversible inhibitor of the MET receptor tyrosine kinase (Liu et al 2011, Baltschukat et al 2019). In preclinical studies, capmatinib treatment induced tumor regression in cancer models with MET exon 14 skipping mutation, MET amplification, MET overexpression, or HGF-mediated autocrine MET activation (Liu et al 2011, Baltschukat et al 2019).

Besides the role of MET in cancer, pre-clinical studies suggest that MET and its ligand hepatocyte growth factor (HGF) also function in immune cells, where MET activity leads to immunosuppression (Molnarfi et al 2015). Several mechanisms of MET/HGF-mediated immune suppression have been reported. For example, HGF was found to attract immunosuppressive MET-positive neutrophils to tumor and draining lymph nodes, which can be prevented by inhibition of MET on neutrophils using capmatinib (Glodde et al 2017).

In addition, activation of MET through HGF was found to drive the differentiation of dendritic cells towards a "tolerogenic" (i.e. immunosuppressive) phenotype (Rutella et al 2006), suggesting that MET inhibition could have a positive immunomodulatory effect on the activation of T cells by dendritic cells. Furthermore, it has also been reported that MET is expressed on a subset of cytotoxic T lymphocytes, suppressing their function when activated by HGF (Benkhoucha et al 2017). These observations demonstrate an immunomodulatory potential of MET and HGF by directly acting on immune cells, irrespective of MET dysregulation in the tumor. Consequently, MET inhibitors may restore immune cell function.

In support of this concept, two independent studies (Glodde et al 2017 and RD-2017-00370) using syngeneic mouse models representing several cancer types revealed that capmatinib can enhance T cell-mediated antitumor immunity when combined with anti-PD1 or other immuno-oncology regimens. Importantly, capmatinib single agent activity was minimal or absent in all tested models. The capmatinib + anti-PD1 studies carried out at Novartis RD-2017-00370 showed that combination treatment led to increased T cell infiltration as well as a higher cure rate than either single agent. Higher cure rates were also seen by (Glodde et al 2017), who proposed a reactive production of HGF in the inflamed tumor microenvironment, which led to recruitment of immunosuppressive MET-positive neutrophils. Prevention of this negative feedback loop by capmatinib was suggested to explain the combination benefit. However, the additional mechanisms involving MET-positive immune cells discussed above could also contribute to the observed enhancement of anti-tumor immunity when adding capmatinib to immuno-oncology treatments.

Clinical observations further support the hypothesis that HGF-mediated MET activation is immunosuppressive. In melanoma patients treated with anti-PD1 antibodies, an increase of serum HGF during treatment was seen in a subset of non-responders, but not in responders (Glodde et al 2017), which could be indicative of the HGF-mediated immunosuppressive feedback loop that was observed in mouse models. Furthermore, another study found that high baseline levels of serum HGF were associated with worse clinical outcomes of anti-PD1 treatment in melanoma (Kubo et al 2019).

As of 28-Sep-2018, a total of 1253 cancer subjects and 236 non-cancer subjects have received capmatinib. 709 subjects have been treated with capmatinib as a single agent at different doses. The Maximum Tolerated Dose (MTD) for capmatinib as single agent was not reached. The recommended phase 2 dose (RP2D) for capmatinib as a single agent has been determined to be 400 mg twice daily (BID) in tablet formulation. Five hundred and forty-four subjects have been treated with capmatinib in combination therapies. Fourteen clinical studies with capmatinib are currently ongoing and 16 have been completed. Nineteen subjects have experienced 25 Dose Limiting Toxicities (DLTs): 6 subjects were in single agent studies and 13 were in combination studies.

Most of the reported adverse events (AEs) are mild or moderate in severity. The most frequent AEs suspected to be related to capmatinib of any grade reported in the largest single agent trial CINC280A2201 with 302 subjects were peripheral edema (40.4%), nausea (32.8%), increased blood creatinine (19.2%), vomiting (19.2%), decreased appetite (13.2%), fatigue (13.2%), and diarrhea (11.6%), with most of them being Grade 1/2.

The Grade 3/4 AEs suspected to be related to capmatinib in the CINC280A2201 study include peripheral edema (6.3%), increased lipase (5.0%), fatigue (3.3%), increased alanine aminotransferase (4.0%), vomiting (2.0%), nausea (1.7%), hypophosphataemia (1.7%), and increased aspartate aminotransferase (1.7%).

As of 28-Sep-2018, pneumonitis and interstitial lung disease (ILD) have been reported from both capmatinib single agent studies and combination studies with EGFR TKIs (Tyrosine kinase inhibitors), including events with fatal outcomes. In capmatinib single agent study CINC280A2201, 6 patients (2.0%) experienced suspected pneumonitis of any grade. Three patients (1.0%) experienced Grade 3/4 pneumonitis (1 with a fatal outcome) and two patients (0.7%) experienced Grade 3/4 interstitial lung disease and reported as suspected to be related to capmatinib treatment. All patients had multiple contributing factors including prior radiotherapy and prior therapy with checkpoint inhibitors, concurrent progressive disease of NSCLC. Careful monitoring of patients for signs and symptoms of pneumonitis in capmatinib studies is suggested, especially in combination studies with EGFR TKIs.

Recent clinical studies indicate that MET exon 14 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 2017). Based on the primary analysis of INC280A2201 study, single agent capmatinib has been designated with breakthrough therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring MET exon-14 skipping mutations. Overall response rate were 68% (95% CI: 47.6%-84.1%, N=28) for treatment-naive patients, and 41% (95% CI: 28.9%-53.1%, N=69) for previously treated patients. For more information, please refer to the current capmatinib Investigator's Brochure. Overall, preclinical and early clinical data indicate that capmatinib has a manageable safety profile.

Pharmacokinetics (PK) data collected in clinical trials showed that capmatinib is rapidly absorbed after oral administration with a median time to reach maximum drug concentration (Tmax) ranging from 1 to 2 hours for tablets. The elimination half-life estimated from study CINC280X1101 ranged from 3.5 to 6.3 hours across the cohorts. Accumulation in capmatinib exposure following repeated administration of 400 mg BID tablets is low, with geometric mean accumulation ratio of 1.39-fold in the single agent CINC280A2201 study. The mean plasma exposure increase is roughly dose proportional for capmatinib tablet from 200 to 400 mg BID.

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

Capmatinib is a moderate CYP1A2 inhibitor and an inhibitor of P-gp, BCRP and MATE transporter.

When co-administered with the strong CYP3A4 inhibitor itraconazole, capmatinib AUC increased by approximately 40% without any change in Cmax. When co-administered with the strong CYP3A4 inducer rifampicin, capmatinib AUC and Cmax decreased by 66% and 56%, respectively CINC280A2102. These findings suggest that capmatinib is not a sensitive substrate of CYP3A4.For further details, please refer to the latest version of the capmatinib Investigator's Brochure.

1.1.2 Combination of capmatinib with a checkpoint inhibitor

There are several ongoing studies investigating the safety and efficacy of the combination of capmatinib and checkpoint inhibitors. Capmatinib is being studied with nivolumab in NSCLC and with spartalizumab in hepatocellular carcinoma (HCC). These studies have established a safety profile for capmatinib combined with checkpoint inhibitors and demonstrated some preliminary clinical efficacy. Overall, the safety of capmatinib plus nivolumab in study CEGF816X2201C and capmatinib plus spartalizumab in study CINC280X2108 is consistent with the safety profile of single agent capmatinib in study CINC280X2102.

1.1.2.1 Combination of capmatinib and nivolumab

The combination of capmatinib and nivolumab has been explored in the study CEGF816X2201C, an ongoing phase II, open-label, study of capmatinib in combination with nivolumab in adult subjects with advanced NSCLC (either in high cMET, defined as cMET IHC 3+ or IHC 2+ & GCN $\geq$ 5 or MET exon 14 mutations, or low cMET defined as those other than high cMET) who have progressed on standard chemotherapy and have not been treated with anti-PD(L)1 therapies. As of the data cut-off date of 3-Sep-2018, 44 patients (22 male and 22 female) have been enrolled and treated with capmatinib 400 mg BID + nivolumab 3 mg/kg Q2W. The study has demonstrated the combination is safe and the toxicities are manageable. Preliminary data (cutoff by 03-Sep-2018) suggests the combination of capmatinib and nivolumab demonstrated higher 6-month PFS rate than that of historical data in nivolumab single agent or capmatinib single agent studies (CheckMate-057 and INC280X2102) in the high cMET group. Efficacy data (6 months PFS rate) in low cMET group will be analyzed when the data is mature. Efficacy signals shown in both high and low cMET groups warrant further investigation of capmatinib and checkpoint inhibitor combinations in NSCLC.

1.1.2.2 Combination of capmatinib and spartalizumab

CINC280X2108 is a dose escalation and expansion study evaluating the safety and efficacy of capmatinib in combination with spartalizumab (an investigational anti-PD1 antibody). This is an ongoing phase Ib/II, open-label, multi-center study of capmatinib in combination with spartalizumab or spartalizumab alone for the treatment of patients with advanced HCC who have progressed on sorafenib and have not been treated with anti-PD(L)1 therapies.

As of the data cut-off date of 28-Sep-2018, 48 patients were enrolled in all arms of this study. 27 patients were enrolled in the dose escalation (phase Ib) part at three different capmatinib dose levels (all capmatinib tablets): 200 mg BID capmatinib (N=6), 300 mg BID capmatinib (N=10) and 400 mg BID capmatinib (N=11), all in combination with 300 mg Q3W i.v. spartalizumab. The RP2D was determined as capmatinib 400 mg BID and spartalizumab 300 mg Q3W. At the time of the cut-off, eleven patients were enrolled in the spartalizumab single agent arm of the phase II part of the study and 10 patients were enrolled into the

combination arm of capmatinib and spartalizumab. One phase Ib patient from the 400 mg BID capmatinib in combination with spartalizumab 300 mg Q3W cohort experienced a DLT of Grade 3 diarrhea which was suspected to be related to the study treatment. Thirty-seven patients (77.1%) experienced AEs of any grade which were suspected to be related to the study treatment. The most frequent AEs suspected to be related to the study treatment were peripheral edema (29.2%), nausea (18.8%), rash (18.8%), vomiting (18.8%), increased alanine aminotransferase (16.7%), and pruritus (16.7%), with most of them being Grade 1/2. Eighteen patients (37.5%) had Grade 3/4 AEs suspected to be related to study treatment which include increased aspartate aminotransferase (6.3%), nausea (4.2%), increased alanine aminotransferase (4.2%), asthenia (4.2%), increased lipase (4.2%), acute myocardial infarction (2.1%), adrenal insufficiency (2.1%), increased amylase (2.1%), anemia (2.1%), unstable angina (2.1%), increased blood bilirubin (2.1%), dehydration (2.1%), diarrhea (2.1%), peripheral edema (2.1%), hypotension (2.1%), immune-mediated hepatitis (2.1%), lichen planus (2.1%), liver injury (2.1%), neutropenia (2.1%), decreased platelet count (2.1%), pyrexia (2.1%), pruritic rash (2.1%), rash (2.1%), skin ulcer (2.1%), and systemic inflammatory response syndrome (2.1%). Seven patients (14.6%) experienced the following SAEs suspected to be related to the study treatment: acute myocardial infarction, adrenal insufficiency, dehydration, diarrhea, immune-mediated hepatitis, infusion related reaction, pyrexia, rash pruritic, and blurred vision. The combination has been established to be tolerable within a HCC population and the toxicities are manageable. Efficacy data is not mature yet.

1.2 Purpose

Pembrolizumab is approved as monotherapy for the first-line treatment of NSCLC patients whose tumors have a PD-L1 expression ≥ 50% and no EGFR mutation or ALK rearrangement based on the results of KEYNOTE-024 (Reck et al 2016) and KEYNOTE-042 (Mok et al 2019). Capmatinib exhibits immunomodulatory activity in preclinical tumor models irrespective of MET dysregulation. The combination of capmatinib with checkpoint inhibitors has been established to be tolerable and could provide additional clinical benefit compared to the treatment of single agent checkpoint inhibitor. This study will evaluate the efficacy and safety of capmatinib combined with pembrolizumab in comparison to pembrolizumab as first-line treatment for subjects with locally advanced or metastatic NSCLC who have PD-L1 expression ≥ 50% and have no EGFR mutation or ALK rearrangement.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To evaluate the efficacy of capmatinib plus pembrolizumab in comparison to pembrolizumab alone	Progression-free survival (PFS) based on local investigator assessment as per RECIST 1.1
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the anti-tumor activity of capmatinib plus pembrolizumab in comparison to pembrolizumab alone	• Objective response rate (ORR), disease control rate (DCR), time-to-response (TTR) and duration of response (DOR) based on local investigator assessment as per RECIST 1.1 and overall survival (OS)
• To characterize the safety profile of capmatinib plus pembrolizumab and pembrolizumab alone	• Incidence and severity of AEs and SAEs, AEs leading to dose interruption, dose reduction and dose discontinuation
• To characterize the pharmacokinetics of capmatinib and pembrolizumab	• Pharmacokinetic parameters and concentration
• To evaluate the prevalence and incidence of immunogenicity of pembrolizumab	• Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on treatment of pembrolizumab

[redacted]

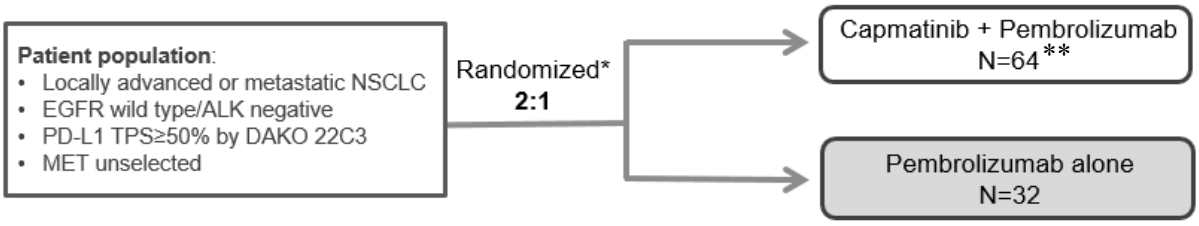
Objective(s)	Endpoint(s)
[redacted]	

3 Study design

This is a randomized, open-label, multicenter, phase II study evaluating the efficacy and safety of capmatinib plus pembrolizumab in comparison to pembrolizumab alone as first line treatment for locally advanced or metastatic non-small cell lung cancer with PD-L1 expression ≥ 50%, MET unselected, EGFR wild type and ALK negative.

The study will enroll approximately 96 subjects in a ratio of 2:1 (capmatinib plus pembrolizumab vs pembrolizumab alone). The study will be stratified by histology (squamous vs non-squamous NSCLC).

Figure 3-1 Study Design



*:Stratified by histology (squamous *versus* non-squamous)

** Following the study enrollment halt, capmatinib treatment has been discontinued in all subjects. Ongoing subjects are treated with pembrolizumab alone.

4 Rationale

4.1 Rationale for study design

The rationale for the study design is described in the table below.

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Randomization and the ratio 2:1	A randomized trial can eliminate bias in treatment assignment. The randomization ratio of 2:1 also increases the chances for subjects to receive the innovative combination of immunotherapy and immunomodulatory agent, which exhibits preclinical/clinical synergistic effect with immunotherapy. It will also allow for increased chance to detect adverse events with the capmatinib and pembrolizumab combination. Furthermore, the analysis power could be increased by utilizing historical data on the control arm.
Randomization stratification factors: Histology (squamous vs. non-squamous)	The stratification factor has been selected to balance potential predictive and/or prognostic factors between the two arms: Although anti-PD-1/PD-L1 activity is observed in both squamous and non-squamous histology, the magnitude of benefit and the absolute outcomes may differ slightly in the two histologies (Brahmer et al 2015, Borghaei et al 2015, Herbst et al 2016, Reck et al 2016, Herzberg et al 2017), therefore randomization is stratified based on tumor histology.

4.2 Rationale for dose/regimen and duration of treatment

The safety of the combination of capmatinib with a checkpoint inhibitor was confirmed in two studies (CINC280X2108 and CEGF816X2201C), and the RP2D of capmatinib was determined as 400 mg *p.o* BID. For details, please refer to Section 1.1.2. No DDI on drug exposure was observed in the two studies.

Pembrolizumab monotherapy has been approved by the FDA and in many countries for advanced/metastatic NSCLC. The recommended dose per pembrolizumab label is 200 mg administered as an intravenous infusion Q3W until disease progression, unacceptable toxicity, or up to 24 months in subjects without disease progression.

The dosing regimen for this study is set at the recommended dose of pembrolizumab and the RP2D of capmatinib as a combination therapy. Subjects will receive study treatment up to 35 cycles (~24 months) or discontinue earlier due to other reasons. Refer to Section 9.1 for details about discontinuation.

4.3 Rationale for choice of combination drugs

Inhibition of MET by capmatinib can enhance T cell mediated antitumor immunity in multiple mouse tumor models treated with anti-PD1 antibodies or other immuno-oncology regimens, as discussed in more detail above (Section 1.1.1; Glodde et al 2017 and RD-2017-00370). While the mechanism underlying this combination benefit has not yet been fully elucidated, several pre-clinical observation suggest an immunosuppressive effect of MET / HGF directly on immune cells, which can be prevented by capmatinib.

Pembrolizumab monotherapy has been approved in many countries for advanced/metastatic NSCLC as first-line treatment. Pembrolizumab demonstrated survival benefit in OS and PFS over chemotherapy (Reck et al 2016, Mok et al 2019), but there is still room for improvement. The combination of capmatinib with checkpoint inhibitors has been established as tolerable and the toxicities are manageable. Preliminary clinical efficacy signals observed in EGF816X2201C study warrant further investigation for this chemotherapy-free regimen in NSCLC. Based on the preclinical and clinical data, combination of capmatinib and pembrolizumab is considered safe and is expected to provide clinical benefit to the subjects in this study.

4.4 Purpose and timing of interim analyses

Following approval of protocol amendment 03, the planned administrative interim analysis will not be performed.

4.5 Risks and benefits

Advanced/metastatic NSCLC is an incurable disease. Patients treated with chemotherapy have a life expectancy of approximately 11-14 months (Gandhi et al 2018, Paz-Ares et al 2018, Mok et al 2019). Recent studies showed pembrolizumab monotherapy demonstrated superior PFS and OS over chemotherapy in patients with PD-L1 $\geq$ 50% and whose tumors do not have EGFR mutation or ALK rearrangement (Refer to Section 1.1). The combination of pembrolizumab with platinum-doublet chemotherapy yields higher response rates compared to pembrolizumab monotherapy, but also produces higher chemotherapy-related toxicities, particularly myelosuppression.

Adding capmatinib to pembrolizumab provides a chemotherapy-free regimen and potential survival benefit for its synergistic anti-tumor effect, which has been seen in preclinical non-MET driven tumor models. The safety profiles of capmatinib and pembrolizumab as monotherapies are well characterized respectively. The combination of capmatinib with checkpoint inhibitors has been established to be tolerable in 2 ongoing studies CINC280X2108 (see Section 1.1.2.2) and CEGF816X2201C (see Section 1.1.2.1).

Risks in this study can be mitigated by subjects complying with eligibility criteria and study procedures, close monitoring for subject safety, and periodic safety data review by the DMC, as specified in Section 10.2. Appropriate eligibility criteria and stopping rules are included in this protocol. Guidance for prophylactic or supportive treatment for expected toxicities, including the management of treatment-related AEs, (e.g. infusion reaction, pneumonitis) are provided in Section 6.5. The risk-benefit ratio is expected to be favorable to the combination therapy.

Following the study enrollment halt, capmatinib treatment was discontinued in all subjects. No additional risk is expected from treatment with pembrolizumab alone in ongoing patients.

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 measures should be permitted/approved by local or regional Health Authorities and Ethics Committees as appropriate.

5 Population

The study population will include adult subjects diagnosed with advanced or metastatic, squamous or non-squamous non-small cell lung cancer (NSCLC), without EGFR or ALK alteration and with PD-L1 high expression (TPS ≥ 50%).

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

5.1 Inclusion criteria

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

1. Must have provided written informed consent prior to any screening procedures
2. Male/female patients ≥ 18 years of age at the time of informed consent. For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.
3. Histologically confirmed and documented locally advanced stage III (not candidates for surgical resection or definitive chemo-radiation) or stage IV (metastatic) NSCLC (per AJCC/IASLC v.8) for treatment in the first-line setting
   - Treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy (other than immunotherapies) is allowed as long as therapy was completed at least 6 months prior to the diagnosis of advanced or metastatic disease.
4. Histologically or cytologically confirmed diagnosis of NSCLC that is both EGFR wild type status and ALK- negative rearrangement status:
   - Subjects with NSCLC of pure squamous cell histology can enter screening without EGFR mutation or ALK rearrangement testing or result; however, patients with pure squamous cell histology who are known to have sensitizing EGFR mutations (such as but not limited to identified in exons 19, 20, or 21) or ALK rearrangements will be excluded.
   - Subjects with known BRAF V600 mutation or ROS-1 rearrangement will be excluded, if required by local guidelines

5. Have an archival tumor sample or newly obtained tumor biopsy with high PD-L1 expression (TPS ≥ 50%) determined by IHC using FDA approved PD-L1 IHC 22C3 PharmDx assay at a local laboratory or at a Novartis designated central laboratory.
    - The archival samples must be most recently available FFPE block or cut tissue sections from the block. Tissue sections must NOT be older than 5 months from the time of sectioning. Archival samples obtained prior to any systemic anti-neoplastic therapy (such as adjuvant therapy) will NOT be acceptable.
    - If local laboratory testing of PD-L1 as described above is not available, a newly obtained tumor biopsy or an archival tumor sample is required to confirm the eligibility.
6. ECOG performance status score ≤ 1
7. Have at least 1 measurable lesion by RECIST 1.1; a previously irradiated lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation
8. Must have recovered from all toxicities related to prior systemic therapy to grade ≤ 1 (CTCAE v5.0). Exception to this criterion: subjects with any grade of alopecia
9. Must have adequate organ function including the following laboratory values at the screening visit:
    - Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L (without growth factor support)
    - Platelets ≥ 100 × 10^9/L (without growth factor support or transfusion)
    - Hemoglobin (Hgb) ≥ 9 g/dL (4 weeks without transfusions or erythropoietin)
    - Calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 45 mL/min
    - Total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) ≤ 3 × ULN
    - Alkaline phosphatase (ALP) ≤ 5.0 × ULN
    - International Normalized Ratio (INR) or Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT) ≤ 1.5 × ULN unless the subject is receiving anticoagulant therapy
    - Asymptomatic serum amylase ≤ grade 2. Subjects 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
    - Fasting plasma glucose ≤ 160 mg/dL (≤ 8.9 mmol/L)
    - Subjects must have the following laboratory values within the laboratory normal limits or corrected to within normal limits with supplements during screening:
        - Potassium
        - Magnesium
        - Phosphorus
        - Total calcium (corrected for serum albumin)

5.2 Exclusion criteria

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

1. Prior treatment with a MET inhibitor or HGF-targeting therapy
2. Prior immunotherapy (e.g. anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).
3. Have known hypersensitivity to any of the excipients of capmatinib (crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes).
4. History of severe hypersensitivity reactions to other monoclonal antibodies, which in the opinion of the investigator may pose an increased risk of serious infusion reaction.
5. Have untreated symptomatic central nervous system (CNS) metastases. Subjects are eligible if CNS metastases have been adequately treated with radiotherapy or surgery and remained stable for >2 weeks after treatment. The subjects must have been off steroids 7 days prior to study treatment
6. Presence or history of a malignant disease, other than NSCLC, that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
7. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e. affecting activities of daily living or requiring therapeutic intervention).
8. Clinically significant, uncontrolled heart diseases.
    - Unstable angina within 6 months prior to screening
    - Myocardial infarction within 6 months prior to screening
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Uncontrolled hypertension defined by a systolic blood pressure (SBP) ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 100 mmHg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening
    - Ventricular arrhythmias
    - Supraventricular and nodal arrhythmias not controlled with medication
    - Other cardiac arrhythmia not controlled with medication
    - QTcF (QT interval corrected by Fridericia's formula) ≥ 470 ms on the screening ECG (as mean of triplicate ECG)
    - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
9. Prior palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment.

10. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting study treatment or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy are not counted as major surgery and subjects can be enrolled in the study ≥ 1 week after the procedure.
11. 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).
12. Concomitant medication(s) with a "Known Risk of Torsades de Point (TdP)" per www.qtdrugs.org that cannot be discontinued or replaced by safe alternative medication.
13. Receiving treatment with strong inducers of CYP3A4 that cannot be discontinued at least 1 week prior to the start of treatment with capmatinib and for the duration of the study.
14. Systemic chronic steroid therapy (>10 mg/day prednisone or equivalent) or any immunosuppressive therapy 7 days prior to planned date of first dose of study treatment. Topical, inhaled, nasal and ophthalmic steroids, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.
15. Participation in a prior investigational study (drug or device) within 30 days prior to first dose of study treatment or within 5 half-lives of the investigational product, whichever is longer, or those who are expected to receive any other investigational drug or device during the conduct of the study.
16. Other severe, acute, or chronic medical or psychotic conditions or laboratory abnormalities that in the opinion of the investigator may increase subject's risk associated with study participation, or that may interfere with the interpretation of study results.
17. Have received or will receive a live vaccination within 4 weeks prior to first dose of study treatment. Seasonal flu vaccines that do not contain live vaccine are permitted.
18. Active hepatitis B or C:
    - Active hepatitis B is defined by positive HBsAg and detectable HBV DNA level in serum by PCR-based method. Subjects with serologic evidence of chronic HBV infection but have an HBV viral load below the limit of quantification can be enrolled with concurrent viral suppressive therapy.
    - Active hepatitis C is defined by quantitative HCV RNA results greater than the lower limits of detection of the assay.
19. Known history of testing positive for Human Immunodeficiency Virus (HIV) infections. For countries where known HIV status is mandatory: test HIV status during screening using a local test.
20. Active, known, or suspected autoimmune disease or documented history of autoimmune disease. Subjects with vitiligo, controlled type I diabetes mellitus on stable insulin, residual autoimmune-related hypothyroidism only requiring hormone replacement, or psoriasis not requiring systemic treatment are permitted.
21. Any other condition that would, in the investigator's judgment, contraindicate subject's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g. intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.

22. Pregnant or breast-feeding (lactating) women, or women who plan to become pregnant or breast-feed during the study, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
23. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during the study and through 120 days after the last dose of pembrolizumab and 7 days after the last dose of capmatinib. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. 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 6 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.
    - Sterilization of the female study subject's male partner, where the male partner was vasectomized at least 6 months before the screening.
    - Use of oral (estrogen and progesterone), injected or implanted combined 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.

    If using oral contraception, women should have been stabilized on the same pill for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate (generally age from 40 to 59 years), history of vasomotor symptoms (e.g. hot flush)) in the absence of other medical justification or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.
24. Sexually active males unless they use a condom during intercourse while taking capmatinib and for 7 days after stopping capmatinib, and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of study treatments via seminal fluid.

    If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).
25. Active infection requiring systemic intravenous therapy.
26. Known history of allogeneic tissue/organ transplantation.

6 Treatment

6.1 Study treatment

In this study, "study treatment" refers to capmatinib plus pembrolizumab or pembrolizumab alone. "investigational drug" refers to the Novartis study drug, capmatinib (INC280).

Pembrolizumab may be considered as "investigational drug" following local regulations.

Novartis Global Clinical Supply (GCS) or its designee will provide capmatinib as 150 mg and 200 mg tablets as individual subject supply, packaged in bottles. Medication labels will comply with the legal requirements of each country and be printed in the local language. Storage conditions are described in the medication label.

Pembrolizumab will be procured or prescribed locally according to local practice and regulations, or supplied by Novartis country organizations. Handling and storage of pembrolizumab will follow the instructions in the package insert.

Following approval of protocol amendment 03, subjects who remain in the study may continue to receive pembrolizumab treatment as per investigator's discretion until unacceptable toxicity, or disease progression, or up to 35 cycles of treatment, whichever occurs first. In countries where pembrolizumab is approved and available for the study indication, subjects may be transitioned to commercial pembrolizumab and discontinued from the study.

6.1.1 Investigational and control drugs

The first dose of study treatment (capmatinib plus pembrolizumab or pembrolizumab alone) is given on Day 1 of Cycle 1. Cycle 1 Day 1 should occur no later than 3 days after randomization registration into the IRT (Interactive Response Technology) system.

All dosages prescribed and administered to subjects and all dose interruptions and changes during the study must be recorded on the study treatment eCRF (electronic Case Report/Record Form). Refer to Section 6.7.2 for study treatment prescribing and administration information.

Table 6-1 Investigational and control drugs

Investigational and control drugs	Pharmaceutical Dosage Form	Route of Administration	Drug package	Supplier (global or local)
Capmatinib (INC280) 150 mg or 200 mg	Film-coated tablet	Oral use	Open-label subject specific; bottles	Global
Pembrolizumab 100mg/4mL (25 mg/mL)	Solution in vial for infusion	Intravenous use	Refer to local drug package	Local
Pembrolizumab 50 mg	Lyophilized powder in vial for reconstitution for infusion	Intravenous use	Refer to local drug package	Local

6.1.2 Additional study treatments

Not applicable.

6.1.3 Treatment arms

Subjects will be assigned to one of the following two treatment arms in a ratio of 2:1. A complete cycle of treatment is defined as 21 days of an infusion of pembrolizumab, with or without continuous capmatinib treatment.

- Capmatinib 400 mg (tablets) orally twice daily (BID) followed by pembrolizumab 200 mg intravenously (i.v.) on day 1 of each cycle, every 21 days.
- Pembrolizumab 200 mg intravenously (i.v.) alone every 21 days.

6.1.4 Treatment duration

Subjects in both treatment arms will receive up to 35 cycles (~24 months) of study treatment. Subjects may be discontinued from study treatment earlier due to other reasons. Refer to Section 9.1 for details about discontinuation.

6.1.4.1 Treatment beyond disease progression

Following approval of protocol amendment 03, treatment with pembrolizumab will strictly adhere to the drug's approved label for the study indication. Accordingly, pembrolizumab may be administered until disease progression, unacceptable toxicity, or up to 35 cycles in subjects without disease progression, whichever occurs first. Treatment beyond disease progression will no longer be allowed as part of this study.

Subjects who have documented disease progression per RECIST 1.1 can remain on study treatment if they meet all the following criteria after documented discussion and agreement between the investigator and the Novartis medical monitor. Subjects are to be informed by the investigator of the options to continue study treatment as well as of other therapeutic options and their benefits, should they exist.

- Clinical benefit per investigator's judgement (e.g. tumor shrinkage at other sites or symptomatic improvement)
- Continuation of treatment beyond initial progression will not delay an imminent intervention to prevent serious complications of disease progression
- Subject exhibits adequate tolerance to study treatment
- Subject performance status is stable
- Absence of symptoms and signs (including worsening of clinically relevant laboratory values) indicating disease progression

Subjects who meet the above criteria and continue study treatment beyond initial disease progression per RECIST 1.1 (see Section 16.1) [redacted] and continue all study procedures as outlined in Table 8-2.

In case of clinical deterioration or suspicion of disease progression, a follow-up imaging assessment should be performed promptly rather than waiting for the next scheduled assessment.

[redacted]

[redacted]

Please refer to Section 8.3 for additional information on RECIST 1.1 [redacted].

6.2 Other treatment(s)

In general, for subjects taking capmatinib, the use of any concomitant medication/therapy deemed necessary for the care of the subject (e.g. such as anti-emetics, anti-diarrhea) is permitted (see Section 6.2.1), except when specifically prohibited (see Section 6.2.2).

For the concomitant/prohibited therapies when taking pembrolizumab, please refer to the locally approved label.

The subject must be told to notify the investigator about any new medications he/she takes after the start of the study treatment. All medications (excluding study treatment), blood transfusions, surgeries and procedures (including physical therapy) administered after the subject has signed inform consent form until 30 days after the last dose of study treatment will be recorded in the appropriate eCRF. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications, food supplements and vitamins.

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

- No other investigational therapy should be given to subjects
- No anticancer agents other than the study treatment (capmatinib and pembrolizumab) should be given to subjects.

6.2.1 Concomitant therapy

6.2.1.1 Permitted concomitant therapy

Subjects are permitted to use the following medications.

- Oral or topical antibiotics
- Medications to prevent or treat nausea, vomiting or diarrhea
- Growth factors (e.g. G-CSF, GM-CSF, erythropoietin, platelets growth factors, etc.) are allowed per investigator's judgement and per local guidelines.
- Treatment with bisphosphonates for pre-existing bone metastases is permitted, if clinically indicated, and following existing local guidelines. Treatment with bisphosphonates should preferably begin before the study treatment is initiated, but can also be initiated during therapy only if absence of radiological bone disease progression is well documented (in this case, the reason for its use must be clearly documented; i.e. "pre-existing, non-progressing, bone metastases").
- Oxygen therapy and blood products or transfusions

- Nutritional support or appetite stimulants
- Pain medication
- Radiotherapy with palliative intent, including but not limited to analgesic purposes or for lytic lesions at risk of fracture, may be carried out if required.

6.2.1.2 Permitted concomitant therapy requiring caution and/or action for the treatment of capmatinib plus pembrolizumab

Capmatinib is a moderate CYP1A2 inhibitor. Coadministration of capmatinib increases sensitive CYP1A2 probe substrate (caffeine) AUC (Area under the curve) by 135% CINC280A2103. The dose of CYP1A2 substrates with narrow therapeutic index may need to be reduced when used concurrently with capmatinib as capmatinib may increase their exposure. Consult the product information of concomitant drug for dose adjustment.

Coadminstration of capmatinib increased Pgp substrate (digoxin) exposure (AUC and Cmax by 47% and 74%, respectively) and breast cancer resistance protein (BCRP) substrate (rosuvastatin) exposure (AUC and Cmax by 108% and 204%, respectively) CINC280A2105. Monitor subjects closely for symptoms of increased exposure to Pgp or BCRP substrates. Consult the concomitant Pgp or BCRP substrate product information when considering dose adjustment.

Coadministrating capmatinib with strong CYP3A4 inhibitor (itraconazole) increases capmatinib AUC by 40%. There is no change in capmatinib Cmax. Execute caution when using a strong CYP3A4 inhibitor concurrently with capmatinib CINC280A2102. The effect of the moderate CYP3A4 inducer, efavirenz, administered at 600 mg q.d. on the single or multiple dose capmatinib PK in patients was simulated using the PBPK model. The model predicted a weak effect of 45% reduction in capmatinib AUC0-12 and 34% reduction in Cmax at steady state DMPK R1701418-Table 6.9.

In healthy subjects, multiple doses of an oral proton pump inhibitor (PPI), rabeprazole at 20 mg once daily resulted in a modest reduction in the extent of capmatinib absorption with a 37.5% decrease in Cmax and a decrease of 25.2% in AUCinf. A similar result was observed in a small number of subjects A2108 with concomitant PPI use. Caution should be exercised during concomitant use with PPIs.

Capmatinib should be taken at least 3 hours before or 6 hours after an H2-receptor antagonist, and at least 2 hours before or 2 hours after an antacid.

Refer to Table 6-2 below for a list of the medications (presented by mechanism of interaction) that require caution when concomitantly used with capmatinib.

Table 6-2 Capmatinib: drugs to be used with caution during co-administration – obsolete upon approval of protocol amendment 03

Mechanism of Interaction	Drug Name
Strong CYP3A inhibitor	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, eltegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
Moderate CYP3A inducer	bosentan, dabrafenib, efavirenz, etravirine, genistein, modafinil, nafcillin, tipranavir/ritonavir, lopinavir, telotristat
CYP1A2 substrate with NTI	theophylline, tizanidine
P-gp substrates	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, atorvastatin, , boceprevir, bosentan, carvedilol, caspofungin, ceritinib, colchicine, cyclosporine, dabigatran, digoxin, docetaxel, doxepin, doxorubicin, eribulin, everolimus, fentanyl, fexofenadine, fidaxomicin, fluvastatin, fosamprenavir, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, linagliptin, linezolid, loperamide, losartan, maraviroc, mirabegron, nadolol, naloxegol, nateglinide, nevirapine, nevirapine, nintedanib, olodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, proguanil, posaconazole, pravastatin, ranolazine, ritonavir, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
BCRP substrates	atorvastatin daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitor	esomeprazole, pantoprazole, omeprazole, lansoprazole, rabeprazole, dexlansoprazole
H2-receptor antagonists	ranitidine, nizatidine, famotidine, cimetidine
Antacids	aluminum hydroxide, aluminum carbonate, calcium hydroxide, calcium carbonate, bismuth subsalicylate

Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies".

This may not be an exhaustive list and will be updated periodically.

NTI: narrow therapeutic index

6.2.2 Prohibited medication

During the course of the study, subjects must not receive other additional investigational drugs, devices, chemotherapy, or any other therapies that may be actively against cancer or that are intended to modulate an immune response, however, limited-field palliative radiotherapy may be allowed as a concomitant therapy (see Section 6.2.1).

For the prohibited medications when using pembrolizumab, the use of systemic steroid therapy (at doses greater than 10 mg/day prednisone or equivalent) and other immunosuppressive drugs is not allowed, except for:

- Prophylactic use for subjects with imaging contrast dye allergy.
- Replacement-dose steroids (defined as 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids) in the setting of adrenal insufficiency.
- Transient exacerbations of chronic inflammatory conditions such as COPD. Steroids must be reduced to 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next treatment with pembrolizumab.
- The treatment of study treatment-related infusion reactions or study treatment-related irAEs. Steroids must be reduced to ≤10 mg/day of prednisone or equivalent dose of corticosteroids prior to the next study treatment administration.

For other prohibited medications for subjects treated with pembrolizumab, please follow local guidelines as per standard of care and product labels.

For subjects treated with capmatinib, strong CYP3A4 inducer (rifampicin) decreases capmatinib AUC by 67% and Cmax by 56% CINC280A2102, and therefore concurrent use of strong CYP3A4 inducers should be prohibited as decreased capmatinib exposure may lead to reduced efficacy.

Drugs with a known risk of TdP are prohibited during treatment with capmatinib plus pembrolizumab. For identification of drugs with known risk of TdP, please refer to www.qtdrugs.org (refer to Table 6-4).

The prohibited medications are listed in the Table 6-3 below.

For the capmatinib plus pembrolizumab treatment, all prohibited medications should not be taken. If a subject is only taking pembrolizumab, the prohibited medications when using pembrolizumab merely need to be prohibited. If a subject is only taking capmatinib, the prohibited medications when using capmatinib merely need to be prohibited.

Table 6-3 Capmatinib: Prohibited medications – obsolete upon approval of protocol amendment 03

Mechanism of Interaction	Drug Name
Strong CYP3A4 inducer	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, 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 (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies"

This may not be an exhaustive list, which will be updated periodically.

Table 6-4 Drugs with a known risk of Torsades de Pointes – obsolete upon approval of protocol amendment 03

TdP Risk	Generic Names
Known	amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib

Check crediblemeds.org/healthcare-providers/drug-list for the most updated list.

This may not be an exhaustive list, which will be updated periodically.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

Prior to dosing, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by a delegate under Novartis supervision, using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

Randomization will be stratified by the subject's histology (squamous vs. non-squamous).

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

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff and persons performing the assessments. The Clinical Trial Team (CTT) will not have access to the randomized treatment from the time of randomization until database lock for the primary analysis. Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: independent biostatistician and programmer who will perform Data Monitoring Committee (DMC) analysis, PK bioanalyst, modeler and modeling programmer. The study bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the samples. The CTT, investigators and site personnel will not have access to any aggregated efficacy and safety results by treatment arm until the primary analysis. While the CTT will have access to the dose administration record, the randomization codes and full randomization list will be kept strictly confidential from the CTT until primary analysis.

Following the enrollment halt, the randomization information was released to the CTT for internal data review and to address Health Authorities' queries.

6.5 Dose escalation and dose modification

Dose escalations are not permitted.

6.5.1 Dose modifications

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

In situations where the causality of toxicity cannot be clearly attributed to one of the study drugs (capmatinib or pembrolizumab), dose modification recommendations for both study drugs should be followed.

There are no dose reductions allowed in this study for pembrolizumab. Dose interruptions for pembrolizumab are permitted. Please refer to local pembrolizumab labels for recommended treatment modifications for pembrolizumab.

For clinical management of suspected immune-related adverse event (irAE) and corresponding dose modification requirements, reference to consensus management guidelines is recommended such as those provided in the National Comprehensive Cancer Network (NCCN) Guidelines for the Management of Immunotherapy-Related Toxicities (available at:

https://www.nccn.org/professionals/physician_gls/default.aspx#immunotherapy), the American Society for Clinical Oncology (ASCO) clinical practice guideline for Management of Immune-Related Adverse Events in Subjects Treated With Immune Checkpoint Inhibitor Therapy (Brahmer et al 2018) or the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Management of Toxicities from Immunotherapy (Haanen et al 2017).

Consider early referral to specialists with expertise in the diagnosis and management of immune-related AEs to thoroughly investigate events of uncertain etiology.

Events not included in the study protocol or the reference guidance documents should be managed per institutional preference.

Dose reductions and interruptions are permitted for capmatinib. These dose modifications are summarized in Table 6-6. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation for capmatinib is mandatory for specific events indicated as such in Table 6-6.

Capmatinib dose reduction will follow the dose reduction steps described in Table 6-5 . For each subject, a maximum of two dose level modifications are allowed after which the subject must be discontinued from treatment with capmatinib. The lowest dose allowed, 200 mg BID 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 subject must discontinue treatment with capmatinib if, after treatment is resumed at the lowest allowed dose (200 mg BID), the toxicity recurs with the same or worse severity despite use of maximal preventive measures as per the institution guidelines for toxicity prevention and management.

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

Any planned variance from the guidelines in Table 6-6, in view of subject safety (unless there is an urgent need for action) when in the opinion of the investigator the subject continues to derive clinical benefit, should first be discussed and approved by the Novartis medical monitor.

Overall, AEs are to be graded according to NCI-CTCAE v5.0 (http://ctep.cancer.gov). All dose reductions and interruptions and the reason for the dose reductions/interruptions must be documented in the eCRF.

Table 6-5 Dose reduction steps for capmatinib – obsolete upon approval of protocol amendment 03

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

Table 6-6 Criteria for dose reduction / interruption and re-initiation of capmatinib treatment for adverse drug reactions – obsolete upon approval of protocol amendment 03

Dose modifications for capmatinib	
Worst toxicity CTCAE[a] Grade	**During a cycle of therapy**
No toxicity	Maintain dose level
HEMATOLOGICAL	
Neutrophil count decreased (ANC) Neutropenia	
Grade 1 (ANC < LLN - 1500/mm^3; < LLN - 1.5 × 10^9/L)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3; < 1.5 - 1.0 × 10^9/L)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3; < 1.0 - 0.5 × 10^9/L)	Interrupt dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If not resolved within 7 days, then ↓ 1 dose level
Grade 4 (ANC < 500/mm^3; < 0.5 × 10^9/L)	Interrupt dose until resolved to ≤ grade 2 and then ↓ 1 dose level
Platelet count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75,000/mm^3; < LLN - 75 × 10^9/L)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3; < 75 - 50 × 10^9/L)	Maintain dose level
Grade 3 (PLT < 50,000 -25,000/mm3; < 50 – 25 × 10^9/L)	Interrupt dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, then maintain dose level If not resolved within 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm^3; < 25 × 10^9/L)	Interrupt dose until resolved to ≤ grade 2, then ↓1 dose level
Febrile neutropenia (Grade 3: ANC < 1000/mm^3 38.3°C or a sustained temperature of ≥38°C for more than one hour; Grade 4: Life-threatening consequences; urgent intervention indicated)	Interrupt dose, then: If resolved in ≤ 7 days, resume treatment at ↓ 1 dose level If not resolved within 7 days, discontinue subject from study drug treatment
Hemoglobin decreased (Anemia)	

Dose modifications for capmatinib	
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)	Interrupt 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	Interrupt dose until resolved to ≤ grade 2 and then ↓ 1 dose level If toxicity recurs, discontinue subject from study drug treatment.
RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 × ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 × ULN)	Interrupt dose until resolved to ≤ grade 1 or baseline, then resume treatment at the same dose level.
Grade 3 (> 3.0 - 6.0 × ULN)	Interrupt dose until resolved to ≤ grade 1 or baseline, then resume treatment at ↓ 1 dose level.
Grade 4 (> 6.0 × ULN)	Permanently discontinue subject from study drug treatment
HEPATIC	
Isolated Total Bilirubin elevation*	
Grade 1 (> ULN - 1.5 × ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 × ULN)	Interrupt dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, maintain dose level If not resolved within 7 days, ↓1 dose level
Grade 3 (> 3.0 - 10.0 × ULN)	Interrupt dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days, permanently discontinue subject from study drug treatment
Grade 4 (> 10.0 × ULN)	Mandatory: Permanently discontinue subject from study drug treatment
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3 × ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 × ULN)	Maintain dose level Or consider to interrupt dose until resolved to ≤ grade 1, then maintain dose level
Grade 3 (> 5.0 - 20.0 × ULN)	Interrupt 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

Dose modifications for capmatinib	
	If not resolved within 7 days, resume treatment at ↓ 1 dose level
Grade 4 (> 20.0 × ULN)	Mandatory: Permanently discontinue subject from study drug treatment
Combined elevations of AST or ALT and Total Bilirubin[b,c,d]	
For subjects with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 × ULN combined with total bilirubin >2.0 × ULN without evidence of cholestasis OR For subjects with elevated baseline AST or ALT or total bilirubin value: (AST or ALT > 2 × baseline AND > 3.0 × ULN) OR (AST or ALT >8.0 × ULN), whichever is lower, combined with (total bilirubin >2 × baseline AND > 2.0 × ULN)	Mandatory: Permanently discontinue subject from study drug treatment
CARDIAC	
Myocarditis or other cardiac event	
Recommended clinical management of myocarditis grade ≥ 2 or other cardiac event grade ≥ 3: Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg QD and consult with a cardiologist (hospitalization as indicated)	
Grade 1	Maintain dose level of study drug treatment (pembrolizumab can be continued)
Myocarditis grade ≥ 2	Permanently discontinue subject from study drug treatment (pembrolizumab should also be discontinued)
Other cardiac event grade ≥ 3	Permanently discontinue subject from study drug treatment (pembrolizumab should also be discontinued)
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTcF 450-480 ms) Grade 2 (QTcF 481-500 ms)	Maintain dose level
Grade 3 (QTcF ≥ 501 ms on at least two separate ECGs)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If not resolved within 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 subject from study drug treatment
GASTROINTESTINAL	
Pancreatitis	
Grade 2	Maintain dose level
Grade ≥ 3	Mandatory: Permanently discontinue subject from study drug treatment
Asymptomatic amylase and/or lipase elevation (If symptomatic elevations of any grade, discontinue CAPMATINIB permanently)	

Dose modifications for capmatinib	
Grade 1 (> ULN - 1.5 × ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 × ULN)	Maintain dose level
Grade 3 (> 2.0 - 5.0 × ULN)	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 × ULN)	Permanently discontinue subject from study drug treatment
Diarrhea**	
Grade 1 (despite appropriate anti-diarrheal medication)	Maintain dose level
Grade 2 (despite maximal anti-diarrheal medication)	Interrupt dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then interrupt dose until resolved to ≤ grade 1, then resume treatment at↓ 1 dose level
Grade 3 or 4 (despite appropriate anti-diarrheal medication)	Interrupt 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)	Interrupt dose until resolved to ≤ grade 1, then maintain dose level.
Grade 3 (despite appropriate anti-emetics)	Interrupt dose until resolved to ≤ grade 1, then↓ 1 dose level
Grade 4 (despite appropriate anti-emetics)	Interrupt dose until resolved to ≤ grade 1, then ↓ 1 dose level
Nausea	
Grade 1 (despite appropriate anti-emetics)	Maintain dose level
Grade 2 (despite appropriate anti- emetics)	Maintain dose level Or consider to interrupt dose until resolved to ≤ grade 1, then maintain dose level
Grade 3 (despite appropriate anti-emetics)	Interrupt 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	Interrupt dose until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, then↓resume treatment at 1 dose level. If not resolved within 7 days (despite appropriate skin toxicity therapy), then discontinue subject from study drug treatment

Dose modifications for capmatinib	
Grade 4, despite skin toxicity therapy	Permanently discontinue subject from study drug treatment
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
ILD/Pneumonitis Monitor subjects for pulmonary symptoms indicative of ILD/pneumonitis. In addition, withhold capmatinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for ILD/pneumonitis to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage.	
Grade 1	Interrupt capmatinib during diagnostic workup for ILD/Pneumonitis. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a diagnosis of ILD/Pneumonitis, study drug may be restarted at the same dose. If it recurs after resumption of study drug permanently discontinue capmatinib.
Grade 2	Mandatory: interrupt capmatinib during diagnostic work up for ILD/pneumonitis until improvement to ≤ Grade 1. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a 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 recur after resumption of study drug at decreased dose, permanently discontinue capmatinib
Grade 3 or 4	Mandatory: permanently discontinuestudy drug. Treat with IV steroids as clinically indicated. Oxygen therapy as indicated
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue/ Asthenia	
Grade 1	Maintain dose level
Grade 2	Maintain dose level Or consider to interrupt dose until resolved to ≤ grade 1, then maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then:

Dose modifications for capmatinib	
	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	Maintain dose level
Grade 2	Maintain dose level Or consider to interrupt dose until resolved to ≤ grade 1, then maintain dose level
Grade 3	Discontinue dose until resolved to ≤ Grade 1, then↓1 dose level
Grade 4	Discontinue CAPMATINIB
Hypersensitivity	
If a suspected hypersensitivity case occurs, investigators should interrupt capmatinib while ruling out other possibilities and evaluating the severity of the patient's hypersensitivity. Management of the symptoms of hypersensitivity should follow Table 6-6 unless investigators decide permanent discontinuation of capmatinib is indicated.	
Other adverse events	
Grade 1 or 2	Maintain dose level, consider to initiate appropriate support medication. For any intolerable grade 2 (e.g.: limiting instrumental ADL), consider omitting the dose until resolved to ≤ grade 1, then↓ 1 dose level.
Grade 3	Interrupt dose until resolved to ≤ grade 2, then↓ 1 dose level
Grade 4	Interrupt dose and then discontinue from study drug treatment
All dose modifications should be based on the worst preceding toxicity. a Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0). b "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold c "Cholestasis" defined as: ALP elevation (> 2.0 × ULN and R value (ALT/ALP in × ULN) < 2.0) in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis d If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction. * Note: If total bilirubin > 3.0 × 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. Please refer to Table 6-7 for recommended medications.	

Dose modifications for capmatinib
*** During the whole duration of treatment with CAPMATINIB, the subject is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing and avoid sunbathing or using a solarium intensively.

6.5.2 Follow-up for toxicities

Following approval of protocol amendment 03, please refer to the locally approved pembrolizumab label and follow each institution's standard of care to ensure adequate monitoring and follow-up of toxicities. The content of Section 6.5.2 below and Table 6-7 are no longer applicable.

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for four weeks, and subsequently at approximately four week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologists, endocrinologists, dermatologists, psychiatrists etc. should be consulted as deemed necessary. All subjects must be followed for AEs and SAEs after discontinuation of pembrolizumab and capmatinib. Recommendations for follow-up evaluations of selected toxicities for subjects receiving capmatinib refer to Table 6-7.

The emergence of irAE may be anticipated based on the mechanism of action of immunomodulatory therapies. Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the investigator locally to verify the immune-related nature of the AE and to exclude alternative explanations.

Subjects whose treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

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

Table 6-7 Follow-up evaluations for selected toxicities – obsolete upon approval of protocol amendment 03

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. Subjects will be instructed to increase hydration until resolution to ≤ CTCAE grade 1 or baseline.

TOXICITY	FOLLOW-UP EVALUATION
HEPATIC	
Isolated total bilirubin elevation	**Total bilirubin CTCAE Grade 1**: Monitor liver function tests (LFTs) per protocol or more frequently if clinically indicated **Total bilirubin CTCAE Grade 2**: Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 ×ULN **Total bilirubin CTCAE Grade 3**: Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 × ULN. If resolved in > 7 days, after discontinuing the subject from capmatinib permanently, the subject should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks **Total bilirubin CTCAE Grade 4**: After discontinuing the subject from capmatinib permanently, the subject should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilization over 4 weeks
Isolated AST/ALT elevation	**AST/ALT CTCAE Grade 2 elevation**: For subjects with baseline value ≤ 3.0 × 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 × ULN For subjects with baseline value > 3.0 - 5.0 × 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 × ULN: • For subjects with baseline value ≤ 3.0 × 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 × ULN • For subjects with baseline value > 3.0 - 5.0 × 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 × ULN For AST/ALT elevation > 10.0 - 20.0 × ULN: Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ baseline

TOXICITY	FOLLOW-UP EVALUATION
	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	Combined elevations of AST or ALT and total bilirubin: After discontinuing the subject 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, GGT (Gamma-glutamyl transferase), total bilirubin (fractionated (direct and indirect), if total bilirubin > 2.0 × ULN), and alkaline phosphatase (fractionated (quantification of isoforms), if alkaline phosphatase > 2.0 × 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: Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Review concomitant medication usage for the potential to inhibit CYP3A4/5 (Table 6-3) and/or to prolong the QT-interval (). Perform a repeat ECG within one hour of the first QTcF of ≥501 ms. If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once daily until the QTcF returns to < 501 ms. Repeat ECGs 7 days and 14 days (and then every 21 days) after dose resumption for all subjects 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 patient with QTcF prolongation should be maintained on study.

TOXICITY	FOLLOW-UP EVALUATION
GASTROINTESTINAL	
Diarrhea	Investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity). The subject 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. For the treatment of diarrhea, it is recommended to follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004). For example: For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at a standard dose (e.g. initial administration of 4 mg, then 2 mg every 2-4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures should be considered. Note: complicating signs or symptoms include: moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration. For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms), management should involve intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg sub-cutaneous t.i.d or 25 to 50 µg IV) and antibiotics (e.g. fluoroquinolone) should be given. Subjects needing loperamide should be followed for side effects of loperamide as its exposure may be increased in the presence of capmatinib.
Nausea and Vomiting	The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of nausea and/or vomiting and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity). Individualized supportive and anti-emetic treatment should be initiated, as appropriate, at the first signs and/or symptoms of these AEs. In subjects with vomiting, the subject should be monitored for signs of dehydration and instructed to take preventive measures against dehydration. For the treatment of nausea and/or vomiting, it is recommended to follow the ASCO Clinical Practice Guideline (Hesketh et al 2017) or NCCN Clinical Practice Guidelines (NCCN Guidelines Version 1.2019 Antiemesis). Drugs listed as prohibited medication (see Section 6.2.2) should not be used. Aprepitant should be used with caution (see Section 6.2.1.2) for subjects whose nausea and vomiting cannot be managed with other agents permitted on study. Subjects needing aprepitant should be followed for side effects of aprepitant as its exposure may be increased in the presence of capmatinib.

TOXICITY	FOLLOW-UP EVALUATION
SKIN TOXICITY	
Rash and Photosensitivity	
CTCAE grade 1	Consider initiating 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 initiating conservative measures such as leg elevation, compression stockings, and dietary salt modification as clinically indicated
CTCAE grade≥3	Initiate/intensify conservative measures
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
ILD/Pneumonitis	
CTCAE Grade 1	CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression- re-image at least every 3 weeks. Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection. Monitoring of oxygenation via pulse oximetry recommended Consultation of pulmonologist recommended.
CTCAE Grade 2	CT scan (high-resolution with lung windows) • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Pulmonary function tests[a] - if normal at baseline, repeat every 8 weeks • Bronchoscopy with biopsy and/or BAL recommended[c] Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated)[b]
CTCAE Grade 3 or 4	CT scan (high-resolution with lung windows). • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist. • Pulmonary function tests[a]-if abnormal, repeat every 8 weeks until normalized. • 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].

TOXICITY	FOLLOW-UP EVALUATION
	• If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication.
*Note: this table refers only to the evaluation schedule to monitor selected toxicities. Refer to Table 6-5 Dose reduction steps for capmatinib for dose modifications required for applicable toxicities **Note: except if the subject is Grade 2 at baseline in which case: it is ≥ CTCAE grade 3 [a] PFT (Pulmonary function tests) to include: diffusing capacity corrected for hemoglobin (DLCO); spirometry; resting oxygen saturation. Guideline for significant deterioration in lung function: Decrease in spirometry and/or DLCO of 30% and/or O2 saturation ≤ 88% at rest on room air. [b] Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. Consider tapering dosage at end. [c] If bronchoscopy is performed, bronchoalveolar lavage (BAL) should be done where possible to exclude alveolar hemorrhage, opportunistic infections, cell count + determination lymphocyte CD4/8 count where possible. t.i.d = Three times a day.	

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

Subjects with transaminase increase combined with TBIL increase may be indicative of potential DILI and should be considered as clinically important events.

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

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT >3.0 × ULN combined with TBIL > 2.0 × ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: (AST or ALT > 2 × baseline AND > 3.0 × ULN) OR (AST or ALT > 8.0 × ULN), combined with (TBIL > 2 × baseline AND > 2.0 × ULN)

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 × ULN with R value < 2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis.In the absence of cholestasis, these subjects should be immediately discontinued from study treatment, and repeat LFTs as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment, and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, and history of any pre-existing liver conditions or risk factors, should be collected.

Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Capmatinib will be dispensed via IRT as specified in Section 6.7 following the schedule in Table 8-2. When capmatinib is taken orally at home, the investigator must promote compliance by instructing the subject to take the capmatinib exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take capmatinib as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using tablet counts and information provided by the subject. This information should be captured in the source document at each visit.

Pembrolizumab will be administered at the investigational site following the local practice and instructions in package insert. The date and time of all pembrolizumab administrations during the study and any deviations from the protocol treatment schedule will be captured by the investigator staff or delegates in the source document at each administration visit. All pembrolizumab infused and returned must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects in both treatment arms, as detailed in the pharmacokinetics section (Section 8.5.1).

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

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

Capmatinib

A unique medication number is printed on the label of capmatinib.

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

Pembrolizumab

Pembrolizumab will be supplied locally as commercially available by the site pharmacy or by Novartis country organization. Preparation and dispensation should follow the locally approved package insert and local practice.

6.7.1 Handling of study treatment

Study treatment supplied by Novartis must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. Also, for capmatinib provided by Novartis, they will include storage conditions for the study treatment but no information about the subject, except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatments supplied by Novartis in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

The unused study treatments supplied by Novartis can be destroyed at the local Novartis facility or third party, as appropriate, or locally at the site only if permitted by local regulations and authorized by Novartis.

Pembrolizumab supplied locally by investigational sites should be handled following the local practice.

6.7.2 Instruction for prescribing and taking study treatment

All dosages prescribed and dispensed to subjects and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

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

Table 6-8 Dose and treatment schedule

Investigational/ Control Drug	Dose	Frequency and/or Regimen
Capmatinib 150 mg or 200 mg	- 400 mg orally - 2 × 200 mg - If dose is reduced to 300 mg- 2 × 150 mg - If dose is reduced to 200 mg- 1 × 200 mg	Twice daily (21 day cycles)
Pembrolizumab 100 mg/4mL (25 mg/mL)	200mg - 2 × 100 mg vials	Once every 21 days
Pembrolizumab 50 mg (lyophilized)	200 mg- 4 × 50 mg vials	Once every 21 days

Capmatinib

Capmatinib tablets will be administered orally on a continuous twice daily (BID) dosing schedule, from Day 1 until Day 21 of each 21-day cycle. The starting dose of capmatinib will be 400 mg BID (total daily dose: 800 mg) on a flat scale of mg/day and not individually adjusted by weight or body surface area. The investigator must instruct the subject to take the study drug exactly as prescribed.

- Subjects should be instructed to take capmatinib at approximately the same time each day starting from Cycle 1 Day 1. The morning and the evening doses should be taken 12 (± 4) hours apart, although a 12-hour interval is highly recommended. If a dose is not taken within 4 hours of the planned dosing time, the missed dose should not be replaced.
- Subjects should be instructed to swallow the tablets whole and not to chew them.
- Capmatinib can be taken with or without food. Each dose of capmatinib should be taken with a glass of water.
- On days of co-administration of capmatinib with pembrolizumab, the subject should be instructed to take the dose of capmatinib in the clinic. Capmatinib will be administered prior to the pembrolizumab infusion along with its pre-medication (if pre-medication is necessary). The sequence will allow consistent time of daily dosing for capmatinib. Subjects should receive pembrolizumab at least one hour after capmatinib administration.
- On days that blood PK samples are obtained, the subject should take the dose in the clinic after pre-dose PK samples and prior to post-dose PK samples (if applicable), when instructed by the study staff. The exact time of drug administration should be recorded in the appropriate eCRF. If a subject vomits within 4 hours of capmatinib dosing, the time of vomiting should be recorded on the eCRF. If vomiting occurs during the course of treatment, then no re-dosing of capmatinib is allowed before the next scheduled dose.
- During the whole duration of treatment with capmatinib, the subject is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, avoid sunbathing or using a solarium).

The orally administered film-coated tablet formulation will be provided in two strengths of 150 mg and 200 mg free base equivalent. For the list of excipients, please refer to the current capmatinib Investigator's Brochure.

Pembrolizumab

Pembrolizumab (100 mg concentrate for solution for infusion or 50 mg lyophilized power for reconstitution for infusion) will be administered intravenously at 200 mg once every 21 days. Further instructions for the preparation, administration and infusion durations of pembrolizumab should follow the locally approved package insert.

Study treatment schedule adjustment

After the first dose, there will be a ±4-day window for the administration of pembrolizumab in the subsequent cycles. If a dose cannot be administered within the planned window due to any unresolved AEs, the dose on that cycle should be skipped. The subsequent dose should be administered in the next scheduled cycle or when the AE has been resolved/recovered for dose continuation as specified in Section 6.5.1.

In the combination therapy, if one of the study drugs is permanently discontinued due to any unresolved AEs, the other study drug can be continued. For more details of treatment duration, please refer to Section 6.1.4.

If a subject requires a dose interruption of pembrolizumab for >12 consecutive weeks or capmatinib for > 6 consecutive weeks from last dose of the study treatment due to any unresolved AEs related to study drug(s), the subject must discontinue the study drug. However, if the subject is continuously deriving clinical benefit and, in the opinion of the investigator, it is in the subject's best interest to remain on study treatment, the subject may restart the study treatment after documented agreement with Novartis.

7 Informed consent procedures

Eligible subjects 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 subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject 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). Laboratory and radiological studies which were done prior to obtaining consent as part of the subject's clinical standard of care within the acceptable screening window may be used for screening purposes. The process of obtaining informed consent must be documented in the subject 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.

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

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Follow-up Consent for the pregnant subjects
- As applicable, Pregnancy Follow-up Consent for the pregnant partner of male subjects

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 subjects 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.

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

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

8 Visit schedule and assessments

Following approval of protocol amendment 03, the efficacy and safety assessments will be performed as per each institution's standard of care. The assessment schedule in Table 8-2 will no longer be applicable and will be replaced by Table 8-2b.

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

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-2) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

During the course of the study visits, test procedures should occur on schedule whenever possible as per allowable visit windows specified in Table 8-1 below.

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 allowed by local Health Authority and depending on operational capabilities, phone calls or virtual contacts (e.g. tele consult) 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 Allowable visit windows

Visit name	Window
Screening	Day -28 to Day -1
Cycle 1 Day 1	Within 3 days after randomization in IRT
Day 1 of the subsequent cycles	± 4 Days
PK/IG/PD sampling	Refer to tables in Section 8.5.1
Tumor assessments	± 7 Days
EOT	≤ 7 Days after decision of discontinuation of study treatment
Safety follow up assessment	± 7 Days
Survival follow- up	± 14 Days

Table 8-2 Assessment Schedule – obsolete upon approval of protocol amendment 03

Period	**Screening**	**Treatment**								**Follow-up**		
Visit Name	**Screening**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Subsequent cycles (Up to 35 cycles)**	**EOT**	**Safety**	**Disease progression**	**Survival**
Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**-**	**30**	**-**	**Every 12 weeks**
Obtain informed consent	X											
IRT registration	X (Screening & randomization)	X (for capmatinib dispensing only)										
Collection of local PD-L1 expression data	X[1]											
Demography	X											
Inclusion/exclusion criteria	X											
Diagnosis, stage and grade of cancer	X											
Relevant medical history/current medical conditions	X											
Prior anti-neoplastic therapies (medications, surgery, radiotherapy)	X											
Prior/Concomitant Medications	X	X (concomitant medications to be collected from consent until 30 days after last dose of study treatment or start of new antineoplastic medication (ANP), whichever is sooner.										

Period	**Screening**	**Treatment**								**Follow-up**		
Visit Name	**Screening**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Subsequent cycles (Up to 35 cycles)**	**EOT**	**Safety**	**Disease progression**	**Survival**
Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**-**	**30**	**-**	**Every 12 weeks**
Smoking history	X											
Physical Exam	S	S (Refer to Table 8-4)										
Height	X											
Weight	X	X	X	X	X	X	X	X	X			
Vital Signs	X	X	X	X	X	X	X	X	X			
Performance status	X	X	X	X	X	X	X	X	X			
ECG	X	X (If clinically indicated)										
Hematology	X	X	X	X	X	X	X	X	X			
Chemistry	X	X	X	X	X	X	X	X	X			
Coagulation	X	X (if clinically indicated)										
Thyroid panel including free T4 and TSH and total T3 if abnormal thyroid function is suspected	X	X		X		X		X (Every other cycle from Cycle 7)	X			
Urinalysis	X	X (if clinically indicated)										
Hepatitis markers	X	X (if clinically indicated)										
HIV testing if locally required	S	S (if clinically indicated)										
Serum pregnancy test	S[2]								S			

Period	**Screening**	**Treatment**								**Follow-up**		
Visit Name	**Screening**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Subsequent cycles (Up to 35 cycles)**	**EOT**	**Safety**	**Disease progression**	**Survival**
Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**-**	**30**	**-**	**Every 12 weeks**
Urine Pregnancy Test			S	S	S	S	S	S		S		
Tumor evaluation as per RECIST 1.1 [redacted]	X	X (Refer to Table 8-3)										
Adverse Events	X	X										
Obtain Pathology report (if available) if submitting an archival tumor sample	S											
[redacted]												
Capmatinib PK Sampling[7]			X[6]	X	X							
Pembrolizumab PK and Immunogenicity Sampling[7]		X	X	X			X	X (every 6 cycles)	X	X[8]		
Study drug administration pembrolizumab		X	X	X	X	X	X	X				
Study drug administration		X (continuous dosing, BID)										

Period	Screening	Treatment								Follow-up		
Visit Name	**Screening**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Subsequent cycles (Up to 35 cycles)**	**EOT**	**Safety**	**Disease progression**	**Survival**
Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**-**	**30**	**-**	**Every 12 weeks**
Capmatinib												
Antineoplastic therapies since discontinuation of study treatment										X		
Survival follow up												X

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

1. Only applicable for subjects with local PD-L1 TPS data available for study eligibility. The PD-L1 TPS data tested locally should be recorded in eCRF
2. Within 72 hours prior to first dose of study treatment

6. Only the first eight subjects enrolled into the treatment arm with capmatinib need to take the intensive PK samples specified in Table 8-7. Refer to Table 8-8 for the rest of subjects.
7. If subjects experience an SAE or AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained whenever possible
8. Only when subjects who return to the site for safety follow up assessment

Table 8-2b Assessment Schedule – applicable upon approval of protocol amendment 03

Visit Name	Treatment Phase - all cycles until end of study treatment or 35 cycles	EOT	30-Day Safety Follow-up
Adverse Events	X (continuous)		
Concomitant Medications	X (continuous, until 30 days after last dose of study treatment or start of new antineoplastic medication, whichever is sooner)		
Study drug administration pembrolizumab	X (day 1 of every cycle)		
X = assessment to be recorded in the clinical database			

8.1 Screening

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

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

As part of the screening procedures patients PD-L1 status must be established to determine eligibility. If the local lab has available data meeting the criteria outlined in Section 5.1 this may be accepted. In the event data meeting this criteria is not available, the subject's tumor must be tested at a local or central laboratory using the assay specified in Section 5.1.

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

It is permissible to re-screen a subject if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. A new ICF needs to be signed if the investigator chooses to re-screen the subject after a subject has screen failed. A new subject number will be assigned to the subject. The rescreen form will have to be completed in the electronic Case Report Form (eCRF) to provide the original subject number. All required screening activities must be performed when the subject is re-screened for participation in the study. An individual subject may only be re-screened once for the study. Once the number of subjects screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In such case, screen failure subjects will not be permitted to re-screen.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and are subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event (SAE) during the screening phase (see Section 10.1.3 for SAE reporting details). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. If the subject fails to be randomized, the IRT must be notified within 2 days.

Subjects who are randomized but fail to start treatment, e.g. subjects randomized in error, will be considered as early terminators. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Subject demographics/other baseline characteristics

Subject demographics and baseline characteristic data are to be collected from all subjects. Smoking history and relevant medical history/current medical condition present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the appropriate CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

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

Wherever allowable by local laws and regulations, subject race and ethnicity are collected and analyzed to assess the diversity of the study population as required by certain Health Authorities and may be used to identify variations in safety or efficacy due to these factors.

8.3 Efficacy

Following approval of protocol amendment 03, all efficacy assessments are to be performed according to each institution's standard of care, and the requirements detailed in Table 8-3 are no longer mandated. Additional scans may be done at the investigator's discretion. Efficacy data will not be captured on the eCRFs and there will be no central collection of imaging data.

8.3.1 Efficacy assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.2 (Section 16.1) based on RECIST 1.1 (Eisenhauer et al 2009) [redacted]. The imaging assessment collection plan is presented in Table 8-3.

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The local investigator's assessment will be used for the primary endpoint analysis and for treatment decision making. Central review of the imaging data may be performed if deemed necessary.

Table 8-3 Imaging Assessment Collection Plan – not mandated upon approval of protocol amendment 03

Procedure	Screening/Baseline	During Treatment/Follow-up
CT* of the chest and abdomen (with intravenous contrast enhancement)	Mandated	Every 9 weeks through 45 weeks and every 12 weeks thereafter
CT* of pelvis (with intravenous contrast enhancement)	Mandated	Only if lesions were documented at screening; follow the same schedule as CT of the chest and abdomen, or if clinically indicated

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI of the brain	Mandated	Only if lesions were documented at screening; follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated
Whole body bone scan	Mandated	Only if clinically indicated
Localized bone CT, MRI or x-ray	Mandated for any lesions identified on the whole body bone scan that are not visible on the CT/MRI of the chest, abdomen and pelvis	Only if lesions were documented at screening; follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated
CT or MRI of other metastatic sites (e.g., neck)	If clinically indicated	Only if lesions were documented at screening, follow the same schedule as CT/MRI of the chest and abdomen , or if clinically indicated
Photography with scale/ruler (for any skin lesion)	If clinically indicated (for any skin lesions present)	Only if lesions were documented at screening, follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated
*: If CT is not feasible, refer to the below part “Baseline imaging assessment” for details.		

Baseline imaging assessments

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

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 as the baseline images for this study. Any imaging assessments obtained after randomization will not be considered baseline. Refer to Table 8-3 for a list of imaging assessments required at baseline.

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 (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

Brain MRI or CT must be completed at baseline. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

A whole body bone scan should be performed per institutional standard of care (e.g., Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography

(FDG-PET) or sodium fluoride (NaF) PET). Localized CT, MRI or X-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI.

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

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

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

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

Post-baseline imaging assessments

Imaging assessments as described in Table 8-3 should be performed at the time points specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 8-2). Imaging assessments for response evaluation will be performed every 9 weeks (+/- 7 days) through 45 weeks and every 12 weeks (+/- 7 days) thereafter until disease progression, death, lost to follow-up or withdrawal of consent. Imaging assessments should be scheduled using the randomization date as the reference date (not the date of the previous tumor assessment) and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

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

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

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

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.3.2 Appropriateness of efficacy assessments

The efficacy assessments selected are standard for this indication/subject population. Additional information can be found in Section 16.1 and Section 16.2.

8.4 Safety

Following approval of protocol amendment 03, all safety assessments are to be performed according to each institution's standard of care, and the requirements detailed in Table 8-4 and Table 8-6 are no longer mandated. The results of safety assessments will not be captured on the eCRFs. However, clinically significant findings must be recorded as AEs on the eCRFs. Reporting of AEs, including SAEs, will continue to ensure Sponsor's oversight of safety.

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

For details on AE collection and reporting, refer to the AE Section 10.1.1.

Table 8-4 Assessments & Specifications – not mandated upon approval of protocol amendment 03

Assessment	Specification
Physical examination	Physical examination will be performed according to Table 8-2. At Screening and Cycle 1 Day 1 prior to treatment, a complete physical examination will be performed and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and neurological. After Cycle 1 Day 1 onwards, a short physical examination will be performed (it will include the examination of general appearance and vital signs). Clinically relevant findings that were present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant new findings that begin or worsen after informed consent which meet the definition of an Adverse Event must be recorded as an adverse event. For Japan only: oxygen saturation (SpO2) will be measured by pulse oximetry for Japanese subjects every time physical examination is performed as indicated in Table 8-2. The results of SpO2 will be recorded only in the source documentation.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature. They will be measured at screening and at subsequent time points as specified in Table 8-2.
Height and weight	Height will be measured at screening. Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-2.
Performance status	The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale as specified in Table 8-5 following the schedule given in Table 8-2.

Table 8-5 ECOG Performance Status

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

8.4.1 Laboratory evaluations

All laboratory parameters assessed for safety purpose will be evaluated locally. Additional time points should be added as deemed necessary per the investigator's best judgment to make sure the toxicity profile is sufficiently characterized and dose adjustments are performed to safeguard the safety of the subject.

Laboratory values obtained during the screening to assess the subject's eligibility will not be required to be repeated prior to dosing (except serum pregnancy test if not done within 72 hours prior to treatment start, and hematology/chemistry if not done within 7 days prior to treatment start) unless deemed clinically necessary by the investigator and/or required as per local institutional policies. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Table 8-1) except as stated above.

The investigator is responsible for reviewing all laboratory reports for subjects in the study and evaluating any abnormalities for clinical significance.

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

Table 8-6 Laboratory Assessments – not mandated upon approval of protocol amendment 03

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Hematocrit, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other)
Chemistry	Albumin, Alkaline Phosphatase, ALT, Amylase, AST, Calcium, Creatinine, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, GGT, Lipase, Magnesium, Sodium, Potassium, fasting Glucose (non- fasting glucose allowed post-baseline), Blood Urea Nitrogen (BUN) or Urea, Bicarbonate, Uric Acid, Lactate dehydrogenase (LDH), Phosphorus, Creatine kinase, Total Cholesterol
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If dipstick is abnormal then perform local laboratory Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)

Test Category	Test Name
Coagulation	International normalized ratio (INR) or Prothrombin Time (PT), and Activated Partial Thromboplastin Time (APTT) or Partial Thromboplastin Time (PTT)
Thyroid	TSH (Thyroid Stimulation Hormone), Free T4 and total T3 if abnormal thyroid function is suspected
Hepatitis* markers	HBV-DNA, HBsAg, HBsAb, HBcAb (IgG), HCV Ab, HCV RNA-PCR
HIV testing	HIV antibody where locally required
Pregnancy Test	Refer to Section 8.4.3
*If HBsAg, HBsAb and HBcAb are all negative, HBV DNA test is not required; if HCV Ab is negative, HCV RNA test is not required.	

8.4.2 Electrocardiogram (ECG)

Following approval of protocol amendment 03, ECGs are to be performed according to each institution's standard of care.

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Triplicate 12-lead ECGs are to be collected with ECG machines available locally at the site. The individual ECGs should be recorded approximately 2 minutes apart. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each subject. ECGs will be performed at screening and at the discretion of the investigator at any time and as clinically indicated during the study conduct.

For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at screening before administration of study treatment. Any identifier details must be redacted e.g. subject initials, date of birth.

If a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 ms), the ECG is repeated to confirm the diagnosis. If the subject is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

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

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

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants receiving capmatinib to prevent them from fathering a child AND to prevent delivery of capmatinib via seminal fluid to their partner. In addition, male participants receiving capmatinib should not donate sperm for the time period specified in Section 5.2.

In case of a positive urine pregnancy test, additional tests must be performed to confirm pregnancy and if confirmed, the reporting requirements as described in Section 10.1.4, must be followed. If a subject becomes pregnant, study treatment must be stopped immediately. If a pregnancy test (urine or serum) is positive, but the subject is thought not to be pregnant, study drug should be stopped until it is determined that the test was falsely positive, and pregnancy is excluded.

Assessments of Fertility

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:

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

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

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Pharmacokinetics and immunogenicity assessments

Blood samples will be collected from all subjects for the analysis of plasma capmatinib and serum pembrolizumab concentrations, as well as for immunogenicity (IG) analysis. [redacted]

Following enrollment halt and the release of the memorandum on 04-Feb-2021, collection of PK and IG samples is terminated.

8.5.1.1 Pharmacokinetic and immunogenicity blood collection and handling

The exact date and clock times of drug administration and PK blood draw will be recorded on the appropriate eCRF page. If vomiting occurs within 4 hours following capmatinib administration on the day of post dose PK blood sampling, the clock time of vomiting should be recorded in the dosage administration PK eCRF page.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. A total of 3 mL of blood will be collected at specified time points for capmatinib analysis in plasma. Another 6 mL of blood will be collected for pembrolizumab and IG analysis in serum. **Blood samples should be collected from the arm opposite from the investigational drug infusion, or from another site.** Refer to the study's laboratory manual for detailed instructions for the collection, handling, and shipment of PK and IG samples. If subjects experience an SAE or AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained whenever possible. The date and time of the last dose and the time of PK blood draw should be recorded.

8.5.1.2 Pharmacokinetic sampling for capmatinib

PK blood samples for capmatinib are outlined in Table 8-7 and Table 8-8. The subjects who will be involved in the early safety review will collect more extensive PK samples in Cycle 2 compared to subjects who will not be involved in the early safety review. All subjects will provide a pre-dose PK sample and a post-dose PK sample between 1-4 hours on C3D1 and C4D1.

Table 8-7 Capmatinib pharmacokinetic blood collection log for the first 8 enrolled subjects in combination treatment arm – obsolete upon approval of protocol amendment 03

Cycle	Day	Scheduled Time point (h)	Analytes
2	1	Pre-dose[a]	PK
2	1	1 (±10 minutes)	PK
2	1	2 (±15 minutes)	PK
2	1	4 (±30 minutes)	PK
2	1	8 (±2 hours)	PK
3	1	Pre-dose[a]	PK
3	1	Anytime between 1-4h	PK
4	1	Pre-dose[a]	PK
4	1	Anytime between 1-4h	PK
Unscheduled		Anytime	PK

[a] Take samples immediately prior to administration of capmatinib

Table 8-8 Capmatinib pharmacokinetic blood collection log for rest of subjects other than first 8 enrolled subjects in combination treatment arm – obsolete upon approval of protocol amendment 03

Cycle	Day	Scheduled Time (h)	Analytes
2	1	Pre-dose[a]	PK
2	1	Anytime between 1-4h	PK
3	1	Pre-dose[a]	PK
3	1	Anytime between 1-4h	PK
4	1	Pre-dose[a]	PK
4	1	Anytime between 1-4h	PK
Unscheduled		anytime	PK

[a] Take samples immediately prior to administration of capmatinib

8.5.1.3 Pharmacokinetic and immunogenicity sampling for pembrolizumab

Blood samples for pembrolizumab PK and IG analysis will be collected for both capmatinib plus pembrolizumab arm and pembrolizumab alone arm as outlined in Table 8-9. PK and IG samples will be collected also at the end of treatment visit and in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if IG is suspected. After the cut-off for the primary analysis is reached, no additional PK and IG samples will be collected for the subjects still ongoing in the study.

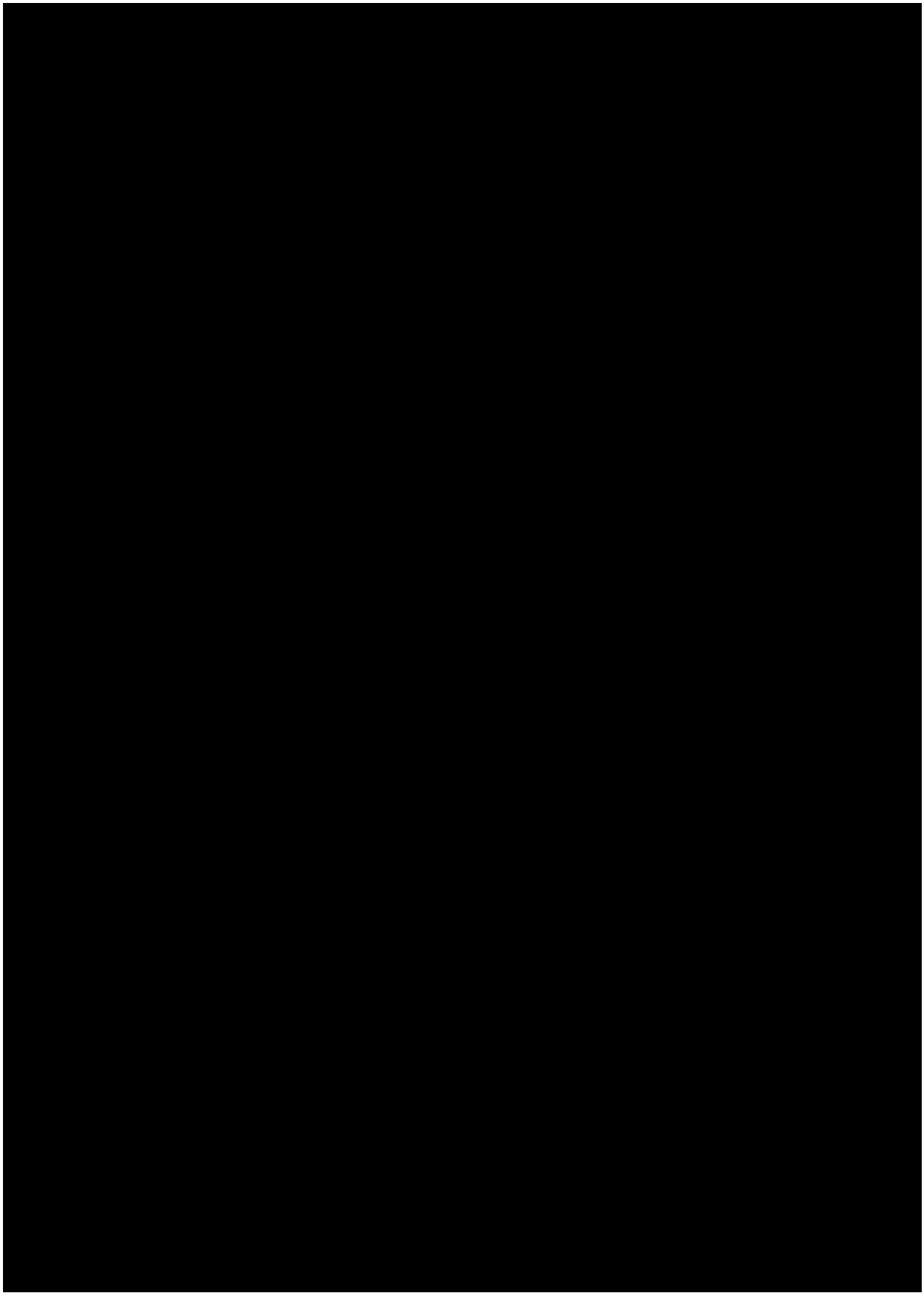
Table 8-9 Pembrolizumab pharmacokinetic and immunogenicity blood collection log – obsolete upon approval of protocol amendment 03

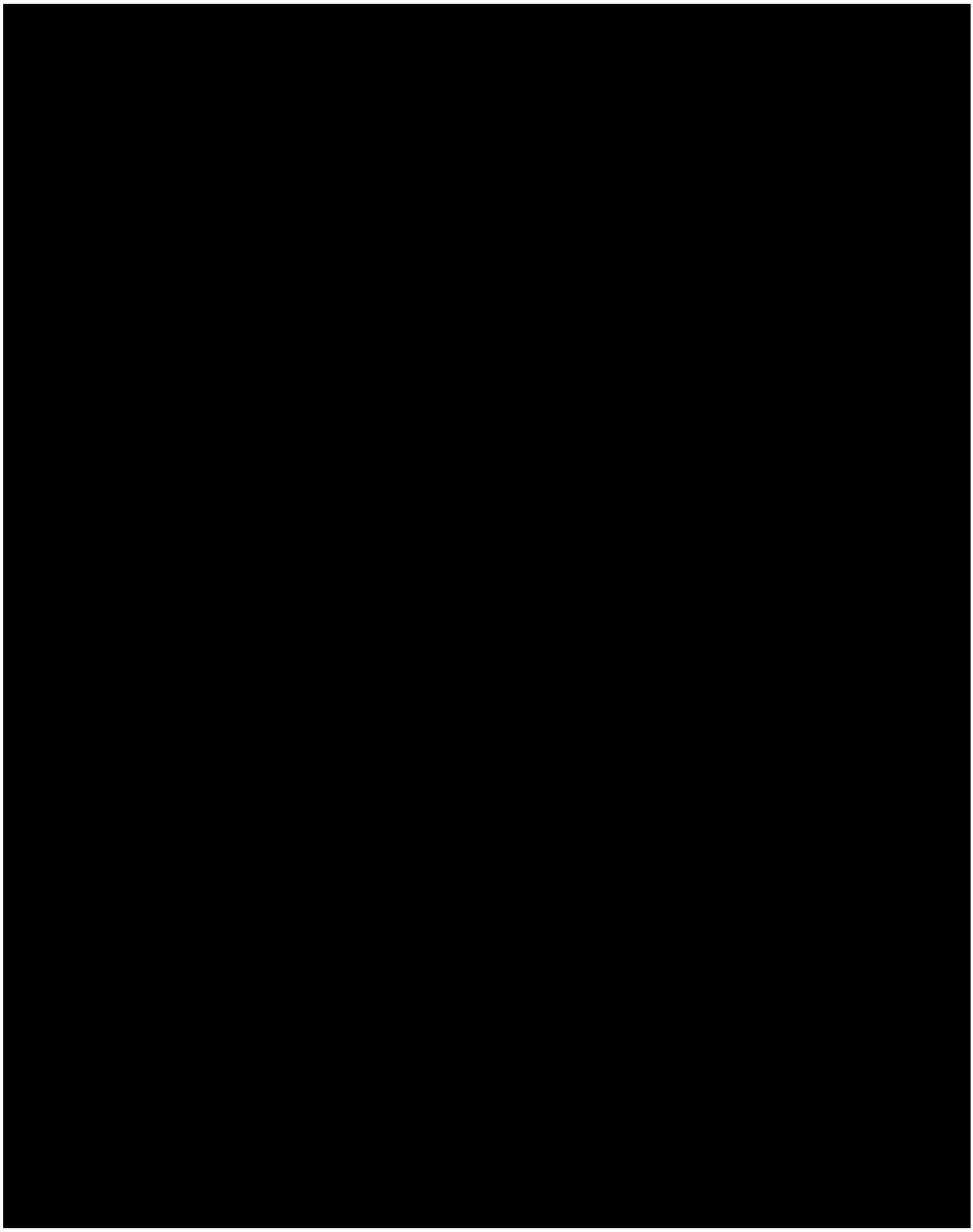
Cycle	Day	Scheduled Time Point (h)	Analytes
1	1	Pre-dose[a]	PK/IG
2	1	Pre-dose[a]	PK/IG
3	1	Pre-dose[a]	PK/IG
6	1	Pre-dose[a]	PK/IG
Every 6 cycles after C6D1 until discontinuation of study treatment	1	Pre-dose[a]	PK/IG
EOT		anytime	PK/IG
30-day safety follow-up[b]		anytime	PK/IG
Unscheduled		anytime	PK/IG

[a] Take samples immediately prior to infusion of pembrolizumab
[b] For subjects who return to the site for safety follow up assessment

8.5.1.4 Analytical method

Pharmacokinetic samples for capmatinib will be quantified using validated LC/MS/MS assays. The assay to quantify and assess the pembrolizumab PK and IG will be a validated homogeneous ELISA (Enzyme-linked immunosorbent assay).





9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject can be initiated by either the subject or the investigator.

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

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Any situation in which study participation might result in a safety risk to the subject.
- Pregnancy
- Death

Following approval of protocol amendment 03, in countries where pembrolizumab is approved and available for the study indication, subjects may be transitioned to commercial pembrolizumab and discontinued from the study.

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

Subjects 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 withdraw of informed consent section). **Where possible, they should return for the assessments indicated** in the assessment schedule. 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 subject/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 subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

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

- new / concomitant treatments
- Adverse events/Serious adverse events.

The investigator must also contact the IRT to register the subject's discontinuation from study treatment of capmatinib. The discontinuation of pembrolizumab is not required to be recorded in IRT.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

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 subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal 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.

For US and Japan: 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 informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects 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.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects 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 subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come in for a final visit) and treated as a prematurely withdrawn subject. 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 subject'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

9.2.1 End of study

Following the study enrollment halt, the end of the study is defined as the earliest occurrence of one of the following:

- discontinued study treatment and completed the safety FU or
- died or
- withdrawn consent or
- been lost to follow-up.

See Section 12 Data Analysis and statistical methods for details of timing of the final reporting of data.

9.2.2 Follow up

9.2.2.1 Safety follow-up

All subjects receiving study treatment must have safety evaluations for 30 days after the last dose of study treatment. The 30 day safety follow-up can be done by telephone call or visit. Concomitant medications will be collected until the 30-day safety follow-up has been completed or the start of a new antineoplastic therapy, whichever occurs first. A PK and immunogenicity sample should be collected at the 30-day safety follow up visit as described in Section 8.5.1. If the 30-day safety evaluation is conducted by phone, samples do not need to be collected.

Data collected should be added to the Adverse Events CRF, the antineoplastic therapies since discontinuation of study treatment CRF, the Concomitant Medications CRF and the PK/IG CRF. For female subjects of child bearing potential, pregnancy tests will be performed as outlined in Section 8.4.3.

As of 04-Feb-2021, collection of PK and IG samples is terminated. Following approval of protocol amendment 03, antineoplastic therapies since discontinuation of study treatment will not be collected.

9.2.2.2 Disease progression follow-up

Following approval of protocol amendment 03, disease progression follow-up will not be performed.

All subjects who discontinue study treatment for any reason other than death or disease progression as per RECIST 1.1 should return for tumor assessments at the intervals specified in Table 8-2 until documented disease progression, death, lost to follow-up or withdrawal of consent (Section 8.3.1).

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient had disease progression. Once the follow-up for disease progression period has ended, the appropriate disposition eCRF should be completed.

9.2.2.3 Survival follow-up

Following approval of protocol amendment 03, survival follow-up will not be performed. Subjects will enter the survival follow-up period once they complete the safety follow-up and/or disease progression follow-up after treatment discontinuation (whichever is longer). Subjects will then be contacted by telephone every 12 weeks to follow up on their survival status. Any new antineoplastic therapies that have been started since the last contact date will also be collected during these phone calls.

Information on all subsequent therapies received for NSCLC, if any, after study treatment has been completed, will be collected (including start date, stop date, and date of progression if any).

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 subject or clinical investigation subject 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 subject 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

1. the severity grade according to the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0.
   - Grade 1 to 4 will be used to characterize the severity of the Adverse Event. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening (corresponding respectively to Grades 1 - 4) will be used.
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes an SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

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

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

6. its outcome

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

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

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 AE 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 assessments must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST 1.1 criteria for solid tumors), should not be reported as a serious adverse event. However, if the progression of malignancy is considered to be related to study treatment as per Investigator's assessment and meets the SAE definition, the event should be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (i.e. deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the investigational drug can be found in the capmatinib Investigator's Brochure or the locally approved package insert of pembrolizumab.

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 subjects 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 an SAE refers to a reaction in which the subject 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 subject's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject 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 subject 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 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 subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 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.

The following SAE reporting time frames apply:

1. Screen Failures (e.g. a subject who is screened but is not randomized): SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.
2. Randomized OR treated Subjects: SAEs collected from a subject signs ICF until 30 days after the subject has discontinued or 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.

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

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

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

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis 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 any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took capmatinib in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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, subject or consumer (EMA definition).

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

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

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

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC), which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be responsible to review safety data. The first review will occur after the first 6 randomized patients have been followed up for at least 6 weeks from randomization or have discontinued earlier. The second review will occur after the first 12 randomized patients have been followed up for at least 6 weeks from randomization or have discontinued earlier. Subsequent reviews on safety data will be conducted every 6 months. The DMC will also assess the data from the interim analysis as mentioned in Section 4.4. The interim analysis (planned and unplanned if any) will be conducted by an independent statistician and independent programmer supporting the DMC. The CTT, investigator staff, persons performing the assessments and subjects will not have

access to the interim data and results of the analysis. However, the key results will be shared by the DMC with a Novartis Committee as specified in the DMC charter.

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

Following the enrollment halt, the randomization information was released for internal data review and to address Health Authorities' queries. As a result, independent data review will not be performed and the DMC will be disbanded.

10.2.2 Steering Committee

A Steering Committee (SC) will be established comprising investigators participating in the trial. 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 the 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 eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

After final database lock, the investigator will receive copies of the subject 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 WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about capmatinib dispensed to the subject and all dosage changes will be tracked using Interactive Response Technology (IRT). The data will be used for analyses specified in Section 12.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. 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 meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis Trial Monitoring 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 subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographics and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on the CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 subjects will be disclosed.

12 Data analysis and statistical methods

The analysis of all primary and secondary endpoints will be performed after the end of the study.

Data from participating centers in this protocol will be combined, so that an adequate number of subjects will be available for analysis. Study data will be reported in the final clinical study report (CSR) based on all subjects' data up to the time of the completion of the study. There will be no additional CSR.

All summaries, listings, figures and analyses will be performed by treatment arm, unless otherwise specified. Additional summaries by histological type (squamous vs. non-squamous) or other subject subgroups may be produced as relevant for selected endpoints.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, distributions (e.g., 25th and 75th percentiles) may also be presented.

Screen failure subjects, as described in Section 8.1, and the reasons for not starting the study treatment will be reported in a listing, but will not be included in any analyses.

Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP). Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

12.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent-to-treat (ITT) principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure. All efficacy endpoints will be analyzed based on the FAS population.

12.1.2 Per-Protocol Set

Not applicable.

12.1.3 Safety Set

The Safety set includes all subjects who received at least one dose of study treatment (either one in the combination arm). Subjects will be classified according to treatment received, where treatment received is defined as:

- the treatment assigned if it was received at least once, or
- the first treatment received when starting therapy with study treatment if the assigned treatment was never received.

All safety endpoints will be analyzed based on the safety set.

12.1.4 Pharmacokinetic Analysis Sets

The capmatinib pharmacokinetic analysis set (INC-PAS) includes all subjects who provide at least one blood sample providing measurable capmatinib PK data. For a concentration to be evaluable, subjects are required to:

- receive the planned treatments prior to sampling
- (for pre-dose samples) not to vomit within 4 hours after the last dosing of capmatinib prior to sampling; (for post-dose samples) not to vomit within 4 hours after the dosing of capmatinib.
- (for pre-dose sample) have the sample collected before the next dose administration and 9-15 hours after the last dose administration.

The pembrolizumab pharmacokinetic analysis set (Pembro-PAS) includes all subjects who provide at least one blood sample providing measurable pembrolizumab PK data. For a concentration to be evaluable, subjects are required to:

- have received one of the planned pembrolizumab treatments prior to sampling.
- (for pre-dose samples) have the sample collected before the next dose administration.
- The immunogenicity (IG) set includes two parts: IG prevalence set and IG incidence set:
- The IG prevalence set includes all subjects in the FAS with a determinant baseline IG sample or at least one determinant post-baseline IG sample.
- The IG incidence set includes all subjects in the IG prevalence set with a determinant baseline IG sample and at least one determinant post-baseline IG sample.

Note: Some subject's data may not be adequate for the reliable estimation of some PK parameters. These cases will be identified and their PK parameters will be excluded from the relevant summaries. The criteria of exclusion will be listed in the SAP.

All endpoints related to pharmacokinetics will be analyzed based on the PAS analysis set, unless otherwise specified.

12.2 Subject demographics and other baseline characteristics

Demographics and other baseline data (including disease characteristics) will be listed and summarized descriptively by treatment arm for the FAS.

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

12.3 Treatments

The Safety set will be used for the analyses below.

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

The duration of exposure will also be presented for each study drug.

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

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by subject and summarized by anatomical therapeutic chemical classification system (ATC) term and treatment arm.

12.4 Analysis of the primary endpoint(s)

12.4.1 Efficacy endpoints

The primary endpoint of this study is the progression-free survival (PFS). Estimation of PFS will be provided by treatment arm, based on the FAS population.

12.4.1.1 Definition of primary endpoint(s)

PFS is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed via local review according to RECIST v1.1 (see Section 16.1 for further details). Censoring conventions are provided below in Section 12.4.1.3.

12.4.1.2 Statistical hypothesis, model, and method of analysis

Kaplan-Meier curves for PFS as well as estimated median PFS along with their two-sided 95% confidence intervals will be presented for each treatment arm. The FAS will be used.

12.4.1.3 Handling of missing values/censoring/discontinuations

PFS will be censored at the date of the last adequate tumor assessment prior to the earliest of analysis cut-off date, the start of a subsequent anti-neoplastic therapy (if any), the date of sponsor's decision to discontinue capmatinib (applicable only to subjects on the combination arm), or if the event occurred after two or more missing tumor assessments. Clinical progression without objective radiological evidence will not be considered as documented disease progression. Subjects should be followed for documented progression after discontinuation of treatment for such clinical progression. The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason has occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred), the date of treatment randomization will be used.

The number of subjects censored and reasons for censoring will be summarized by treatment arm using descriptive statistics.

More details will be provided in the SAP.

12.4.1.4 Sensitivity and Supportive analyses

To further explore the potential lasting effect of capmatinib, a supportive analysis of PFS will be performed without censoring data before the date of sponsor's decision to discontinue capmatinib. Kaplan-Meier curves for such PFS as well as estimated median PFS along with their two-sided 95% confidence intervals will be presented for each treatment arm.

12.5 Analysis of secondary endpoints

The secondary efficacy endpoints are ORR, DCR, TTR, DOR as per RECICT 1.1 and OS.

Estimation of all the secondary endpoints will be provided by treatment arms based on the FAS. All relative listings, tables and figures will be presented by treatment arm, unless otherwise specified.

12.5.1 Efficacy and/or pharmacodynamic endpoint(s)

Objective response rate (ORR)

ORR is defined as the proportion of subjects with a best overall response (BOR) of CR or PR as per local review and according to RECIST 1.1.

BOR is defined as the best response recorded from the start of the treatment until disease progression/recurrence as per local review and according to RECIST v1.1. In particular, any subsequent tumor assessment after the date of sponsor's decision to discontinue capmatinib (applicable only to subjects on the combination arm), will be excluded from the BOR derivation.

In addition, to explore the potential lasting effect of capmatinib, a supportive analysis of BOR will be performed with including tumor assessments after sponsor's decision to discontinue capmatinib.

Disease control rate (DCR)

DCR is defined as the proportion of subjects with a best overall response (BOR) of CR, PR or SD as per local review and according to RECIST 1.1.

Time-to-response (TTR)

TTR applies to all subjects. For responders, TTR is defined as the time from the date of randomization to the first documented response of either CR or PR, which must be subsequently confirmed (although date of initial response is used, not date of confirmation). For non-responders, TTR will be censored at the last adequate tumor assessment date if no PFS event, otherwise, TTR will be calculated as the censored time from the first visit of the first subject to the last visit of the last subject.

Duration of response (DOR)

DOR only applies to subjects for whom best overall response is complete response (CR) or partial response (PR). DOR is defined as the time between the date of first documented response (CR or PR) and the date of first documented progression or death due to underlying cancer.

If progression or death due to any reasons has not occurred by the date of the cut-off, then the subject will be censored following the same rules defined for PFS in Section 12.4.1.3.

Overall survival (OS)

OS is defined as the time from randomization to date of death due to any cause. If a subject is not known to have died by the date of the cut-off, OS will be censored at the last date the subject was known to be alive. Additional considerations may be made for the handling of the patients who continue to receive therapy beyond RECIST v1.1 PD.

ORR and DCR will be summarized along with their accompanying 95% confidence interval. TTR, DOR and OS will be summarized using the Kaplan-Meier estimators for the medians along with their accompanying 95% confidence intervals. Kaplan-Meier curves will also be provided.

Individual lesion measurements, overall response assessments per RECIST 1.1 as well as BOR will be listed by subject and assessment date.

12.5.2 Safety endpoints

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

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

Pre-treatment period:

- from day of subject's first informed consent to the day before first administration of study treatment

On-treatment period:

- Single agent arm: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date).
- Combination arm: from date of first administration of any study drug to 30 days after date of last actual administration of any study drug (including start and stop date).

Post-treatment period:

- Single agent arm: starting at day 31 after last administration of study treatment.
- Combination arm: starting at day 31 after the last administration of study treatment.

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

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

Adverse events

All information obtained on adverse events will be displayed by treatment arm and subject. Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment. Serious adverse events and non-serious adverse events during the on-treatment period will be tabulated. All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths, and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Vital signs

The following will be reported:

- Summary of notable vital sign values

Table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points

12-lead ECG

- 12-lead ECGs including PR, QRS, QT, QTcF intervals and heart rate (HR) will be obtained for each subject during the study. ECG data will be read and interpreted locally.
- A listing of these subjects will be produced (by treatment arm).

Clinical laboratory evaluations

All laboratory data will be listed by treatment arm, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

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

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

For laboratory tests where grades are not defined by CTCAE v5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v5.0

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5.0,

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

In addition to the above-mentioned tables and listings, other exploratory analyses, for example, figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the SAP.

Other safety evaluations

Any other safety information collected will be listed and notable values will be flagged. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

Immunogenicity

Immunogenicity will be characterized descriptively by tabulating anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment. The impact of immunogenicity on PK, safety, and efficacy will be explored. Further details will be specified in the SAP.

12.5.3 Pharmacokinetics

All pharmacokinetic data analysis and PK summary statistics will be based on the PAS population.

Capmatinib and pembrolizumab concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the lower limit of quantification (LLOQ) and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

Pharmacokinetic parameters (e.g. Ctrough, Cmax, AUC) for all PK-evaluable patients will be listed by treatment and subject. For capmatinib, PK parameters include but may be not limited to those listed in Table 12-1. For pembrolizumab, PK parameters will include but may not be limited to Ctrough. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. Missing data will not be imputed and will be treated as missing.

[redacted]

Table 12-1 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable analyte (capmatinib or pembrolizumab) concentration sampling time (tlast) (mass × time × volume^{-1})
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount × time × volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass × volume^{-1})
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)

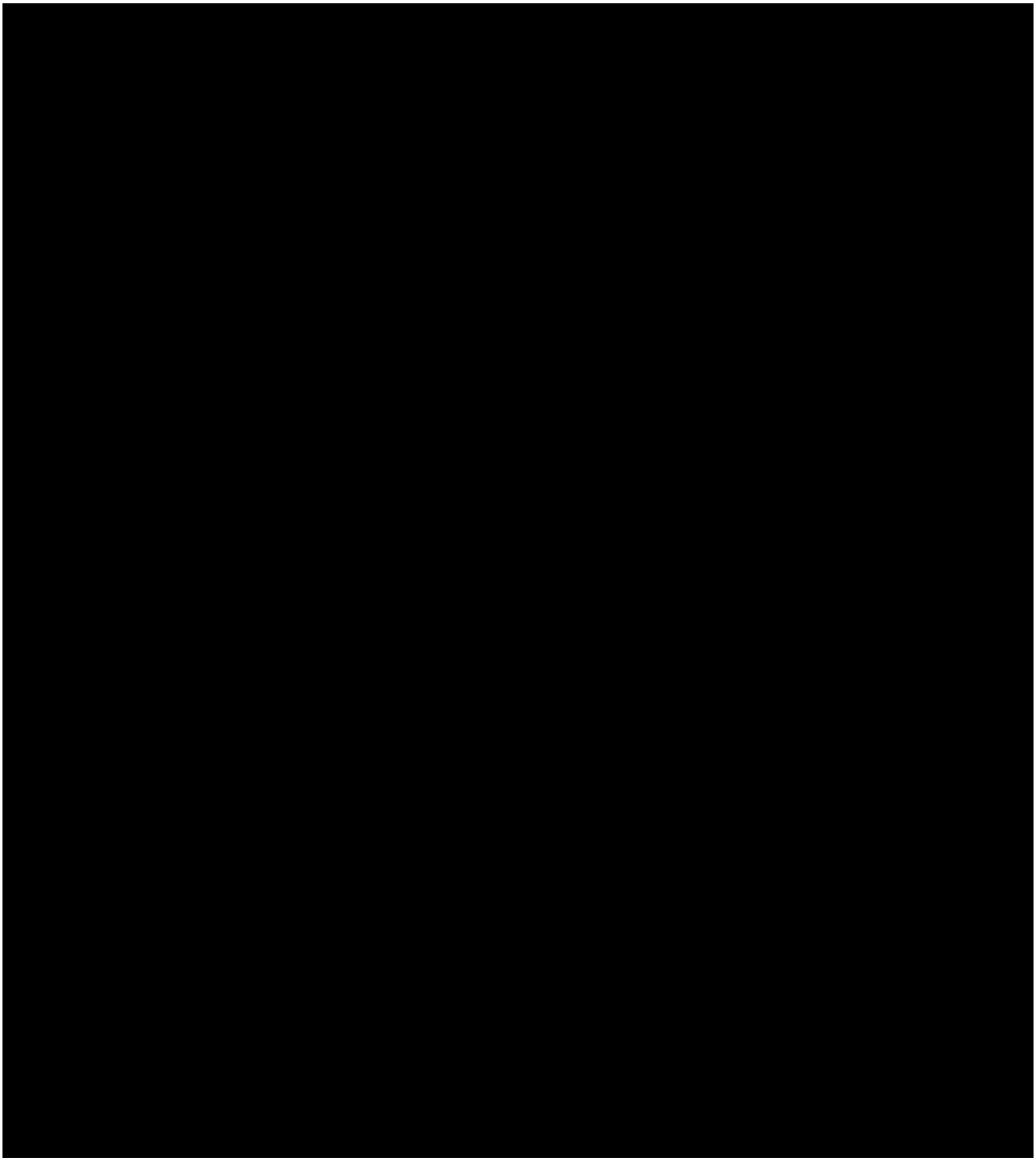
12.5.3.1 Handling of missing values/censoring/discontinuations

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

12.5.3.2 Population pharmacokinetic analysis

If data permit, a mixed-effects model may be applied to the pembrolizumab and/or capmatinib concentration-time data to generate post hoc estimates of pharmacokinetic parameters using software such as NONMEM to characterize pembrolizumab and/or capmatinib exposure. [redacted] Data from this and other studies may be pooled for analysis.

[redacted]



12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

Sample size calculation was based on simulations for various scenarios on treatment outcome, number of subjects included, number of events at the time-point of the originally planned

primary analysis using the Bayesian model defined in Section 16.3, which will no longer be performed.

The evaluation of the success criteria was based on the HR of the PFS (capmatinib plus pembrolizumab vs pembrolizumab alone) after the time-point of risk change in the assumed two-piece exponential distributions (HR2) used in the Bayesian model (in order to account for potential delayed effects).

The success criteria used for the evaluation of the efficacy of the simulation samples are the following:

- At least 50% confidence level that HR2 ≤0.7
- At least 90% confidence level that HR2<1

Approximately 96 subjects will be enrolled in the study, randomized with ratio 2:1 (capmatinib plus pembrolizumab: pembrolizumab alone). In this calculation, a 6% rate of early drop-out before 1st post-baseline assessment as well as a 10% risk of drop-out rate per year on treatment has been taken into consideration.

Regarding the enrolment plan of the study, we assume that 3 subjects will be accrued at the first month after FPFV, 6 at the second, 12 at the third, 14 at the fourth and 15 subject per month for all the following months until approximately 96 subject are enrolled.

The reported median PFS for pembrolizumab alone as first-line therapy for NSCLC subjects with PD-L1≥ 50% was 10.3 months in KEYNOTE-024 study (Reck et al 2016) and 7.1 months in KEYNOTE-042 (Mok et al 2019). It is therefore reasonable to assume that the median PFS of pembrolizumab is between 7.1 and 10.3 months. We expect around 50% reduction in the hazard rate of PFS in capmatinib plus pembrolizumab, after the time-point of risk change in the assumed two-piece exponential distributions.

Table 12-2 presents the operating characteristics of the Bayesian model with different outcome scenarios keeping stable the total sample size (96 subjects) and the number of total PFS events (50) required at the time-point of the primary analysis. With this combination reasonable operating characteristics can be achieved. Description of operating characteristics of alternative sample size can be found in Section 16.3.

Table 12-2 Operating characteristics for scenarios with 96 subjects and 50 events at the primary analysis

Scenarios (Capmatinib plus pembrolizumab vs. pembrolizumab) PFS in months (Hazard ratio)	**Probability of Success**
7.1 vs. 7.1 months (HR2=1)	**0.110**
8.5 vs. 8.5 months (HR2=1)	**0.160**
10.3 vs. 10.3 months (HR2=1)	**0.196**
12.8 vs. 8.5 months (HR2=0.598)	**0.716**
12 vs. 7.1 months (HR2=0.505)	**0.850**
15 vs. 8.5 months (HR2=0.496)	**0.855**
18.5 vs. 10.3 months (HR2=0.501)	**0.840**

HR2: Hazard ratio after the risk change in the two-piece exponential distributions

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, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. 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.

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 subjects 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 subject 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request.

Alimta®SmPC (2009) https://www.ema.europa.eu/documents/product-information/alimta-epar-product-information_en.pdf. Accessed on 10-November-2018.

Alimta®USPI (2004) Available from http://pi.lilly.com/us/alimta-pi.pdf (Accessed on 10-Jul-2018).

American Community Survey 2012-2013 (2012) Available from https://www.census.gov/data/developers/data-sets/acs-3year.html (Accessed on 10-Jul-2018).

Antonia SJ, Villegas A, Daniel D, et al (2018) Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med; 379(24):2342-50.

Baltschukat S, Engstler BS, Huang A, et al (2019) Capmatinib (INC280) Is Active Against Models of Non-Small Cell Lung Cancer and Other Cancer Types with Defined Mechanisms of MET Activation. Clin Cancer Res; 25(10):3164-75.

Benkhoucha M, Molnarfi N, Kaya G, et al (2017) Identification of a novel population of highly cytotoxic c-Met-expressing CD8+ T lymphocytes. EMBO Rep.; 18(9): 1545-58.

Benson AB, Ajani JA, Catalano RB, et al (2004) Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J. Clin. Oncol: 22(14):2918-26.

Borghaei H, Paz-Ares L, Horn L, et al (2015) Nivolumab versus Docetaxel in Advanced Non-squamous Non-Small-Cell Lung Cancer. N Engl J Med; 373(17):1627-39.

Brahmer JR, Hammers H, Lipson EJ (2015) Nivolumab: targeting PD-1 to bolster antitumor immunity. Future Oncol; 11(9):1307-26.

Brahmer JR, Lacchetti C, Thompson JA (2018) Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline Summary. J Clin Oncol; 36(17):1714-68.

Carbone DP, Reck M, Paz-Ares L, et al (2017) First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med; 2415-26.

Cedrés S, Felip E, Cruz C, et al (2018) Activity of HSP90 Inhibiton in a Metastatic Lung Cancer Patient With a Germline BRCA1 Mutation. J Natl Cancer Inst; 110(8):914-7.

Christensen JG, Burrows J, Salgia R (2005) c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. Cancer Lett; 225(1):1-26.

Curran WJ Jr, Paulus R, Langer CJ, et al (2011) Sequential vs concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. Natl Cancer Inst; 103(19):1452-60.

Drilon A (2016) MET Exon 14 Alterations in Lung Cancer: Exon Skipping Extends Half-Life. Clin Cancer Res; 22(12):2832-4.

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

Ferlay J, Soerjomataram I, Dikshit R, et al (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer; 136(5):E359-86.

Frampton GM, Ali SM, Rosenzweig M, et al (2015) Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov; 5(8):850-9.

Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al (2018) Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N. Engl. J. Med.; 378: 2078-92.

Glodde N, Bald T, van den Boorn-Konijnenberg D, et al (2017) Reactive Neutrophil Responses Dependent on the Receptor Tyrosine Kinase c-MET Limit Cancer Immunotherapy. Immunity; 47(4):789-802.e9.

Haanen JBAG, Carbonnel F, Robert C, et al (2017) Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol ; 28(4): iv119-iv142.

Hellmann MD, Ciuleanu TE, Pluzanski A, et al (2018) Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med; 378: 2093-104.

Herbst RS, Baas P, Kim DW, et al (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet; 387(10027):1540-50.

Herzberg B, Campo MJ, Gainor JF, et al (2017) Immune Checkpoint Inhibitors in Non-Small Cell Lund Cancer. Oncologist; 22(1):81-8

Hesketh PJ, Kris MG, Basch E, et al (2017) Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology; 35: 3240-61.

Jenkins RW, Oxnard GR, Elkin S, et al (2015) Response to Crizotinib in a Patient With Lung Adenocarcinoma Harboring a MET Splice Site Mutation. Clin Lung Cancer; 16(5):e101-4.

Jotte RM, Cappuzzo F, Vynnychenko I et al (2018) IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. ASCO Abstract #LBA9000.

Kubo Y, Fukushima S, Inamori Y, et al (2019) Serum concentrations of HGF are correlated with response to anti-PD-1 antibody therapy in patients with metastatic melanoma. J Dermatol Sci; 93(1):33-40.

Langer CJ, Gadgeel SM, Borghaei H, et al (2016) Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol; 17(11): 1497-508.

Liu H, Wu Q, Liu Y, et al (2015) Prognostic significance of β1,6-Nacetylglucosaminyltransferase V expression in patients with hepatocellular carcinoma. Jpn. J. Clin. Oncol; 45:844-53.

Liu X, Wang Q, Yang G, et al (2011) A novel kinase inhibitor, INCB28060, blocks c-MET dependent signaling, neoplastic activities, and cross-talk with EGFR and HER-3. Clin Cancer Res.; 17(22): 7127-38.

Maeda R, Yoshida J, Hishida T, et al (2010) Late recurrence of non-small cell lung cancer more than 5 years after complete resection: incidence and clinical implications in patient follow-up. Chest; 138(1): 145-50.

Mendenhall MA, Goldman JW (2015) MET-Mutated NSCLC with Major Response to Crizotinib. J Thorac Oncol; 10(5): e33-4.

Mok T, Wu Y, Kudaba I, et al (2019). Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet; 393(10183):1819-30.

Molina JR, Yang P, Cassivi SD, et al (2008) Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc; 83(5): 584-94.

Molnarfi N, Benkhoucha M, Funakoshi H, et al (2015) Hepatocyte growth factor: A regulator of inflammation and autoimmunity. Autoimmun Rev.; 14(4): 293-303.

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Control Clin Trials; 9(1):11-8.

NCCN (v5, 2019) Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer.

Novello S, Barlesi F, Califano R, et al (2016) Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol; 27(5):v1-v27.

O'Rourke N, Roqué I Figuls M, Farré Bernadó N, et al (2010) Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev; 6::CD002140.

Paik PK, Drilon A, Fan PD, et al (2015) Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. Cancer Discov; 5(8): 842-9.

Paz-Ares L, Luft A, Vicente D, et al (2018), Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med; 379: 2040-51.

Reck M, Rodríguez-Abreu D, Robinson AG, et al (2016) Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med; 375(19):1823-33.

Rittmeyer A, Barlesi F, Waterkamp D, et al (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet; 389(10066):255-65.

Rutella S, Danese S, Leone G (2006) Tolerogenic dendritic cells: cytokine modulation comes of age. Blood; 108(5):1435-40.

Sause W, et al (2000) Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest; 117:358-64.

Schuler MH, Berardi R, Lim WT, et al (2016) Phase I Study of the Safety and Efficacy of the cMET Inhibitor Capmatinib (INC280) in Patients With Advanced cMET+ Non-small Cell Lung Cancer p. suppl; abstr 9067.

Siegel RL, Miller KD, Jemal A. (2019) Cancer statistics, 2019. CA Cancer J Clin; 69(1):-34.

Socinski MA, Jotte RM, Cappuzzo F, et al (2018) Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med; 2288-301.

The Cancer Genome Atlas (TCGA) Research Network (2014) Comprehensive molecular profiling of lung adenocarcinoma (2014). Nature; 511(7511):543-50.

Waqar SN, Morgensztern D, Sehn J (2015) MET Mutation Associated with Responsiveness to Crizotinib. J Thorac Oncol; 10(5): e29-31.

Wolf J, Han J, Nishio M, et al (2017) GEOMETRY Mono-1: Phase II, Multicenter Study of MET Inhibitor Capmatinib (INC280) in EGFR Wt, MET-Dysregulated Advanced NSCLC p. poster.

16 Appendices

16.1 Appendix 1: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

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
Authors (Version 3.2):	[redacted]
Authors (Version 3.1):	[redacted]
Authors (Version 3):	[redacted]
Authors (Version 2):	[redacted]
Authors (Version 1):	[redacted]

Glossary

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

16.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 16.1.2 and the definition of best response in Section 16.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and res for determination of best response. Section 16.1.3.2 is summarizing the “time to event” variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 16.1.4.1 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP to provide further details needed for programming.

16.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

16.1.2.1 Definitions

16.1.2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

Measurable disease - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 16.1.3.2.9.

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

16.1.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations. Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.1.3.2.8.

16.1.2.2 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up.

- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  - Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
  - Physical exams: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10 mm size, and can be assessed using calipers.
  - Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
  - Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
  - Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

16.1.2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- Target lesions: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 16.1.2.1.1.
- **Nodal target**: See Section 16.1.2.1.1.

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

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

16.1.2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 16-1) and non-target lesions (Table 16-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-3) as well as the presence or absence of new lesions.

16.1.2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number

Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

16.1.2.4.2 Determination of target lesion response

Table 16-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm [2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]
SOD for CR may not be zero when nodal lesions are part of target lesions Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.1.2.2).	

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the “0 mm” recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters).
  Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.

- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the “merged lesion” should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the “merged lesion” should be recorded for the size of one of the original lesions while a size of “0”mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion “reappears” or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.1.2.4.3 Determination of non-target lesion response

Table 16-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK):	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline[2].
1. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail. 2. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)	

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).

- Unequivocal progression: To achieve “unequivocal progression” on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of “Worsened”. Where possible, similar rules to those described in Section 16.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.1.2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 16.1.2.5).
- A **lymph node is considered as a “new lesion”** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.

FDG-PET: can complement CT scans in assessing progression (particularly possible for ‘new’ disease). See Section 16.1.2.2.

16.1.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 16-3.

Table 16-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD1, 2
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. This overall lesion response also applies when there are no non-target lesions identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 16.1.2.4

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

16.1.3 Efficacy definitions

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

16.1.3.1 Best overall response

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

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

excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol

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

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

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.
- The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:
- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 7 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

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

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

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥ 30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline

at the next assessment (but not ≥ 20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

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

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

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of (Dent and Zee 2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

16.1.3.2 Time to event variables

16.1.3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

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

16.1.3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

16.1.3.2.3 Time to progression

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

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

16.1.3.2.5 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

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

16.1.3.2.6 Duration of response

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

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed) the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

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

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

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

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

Assessment date

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

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

Start dates

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

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

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 16.1.3.2.8).

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

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

16.1.3.2.9 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 16-4.

Table 16-4 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 16.1.2.4.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

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

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

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

16.1.3.2.10 Sensitivity analyses

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

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

Table 16-5 Options for event dates used in PFS, TTP, 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 (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1. Definitions can be found in Section 16.1.3.2.7.
2. After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.1.3.2.7.
3. The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

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

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

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

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

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

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

16.1.4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

16.1.4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

16.1.4.2 End of treatment phase completion

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

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

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

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

16.1.4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.1.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the

quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

16.1.4.5 Programming rules

The following should be used for programming of efficacy results:

16.1.4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

16.1.4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 16.1.3.2.8). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

16.1.4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

16.1.4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

16.1.4.5.5 Study/project specific programming

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

16.1.4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 16-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 16.1.3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

16.1.5 References (available upon request)

Dent S, Zee B (2001) Application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19:785-91.

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

Ellis S, Carroll KJ, Pemberton K (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials; 29(4): 456-65.

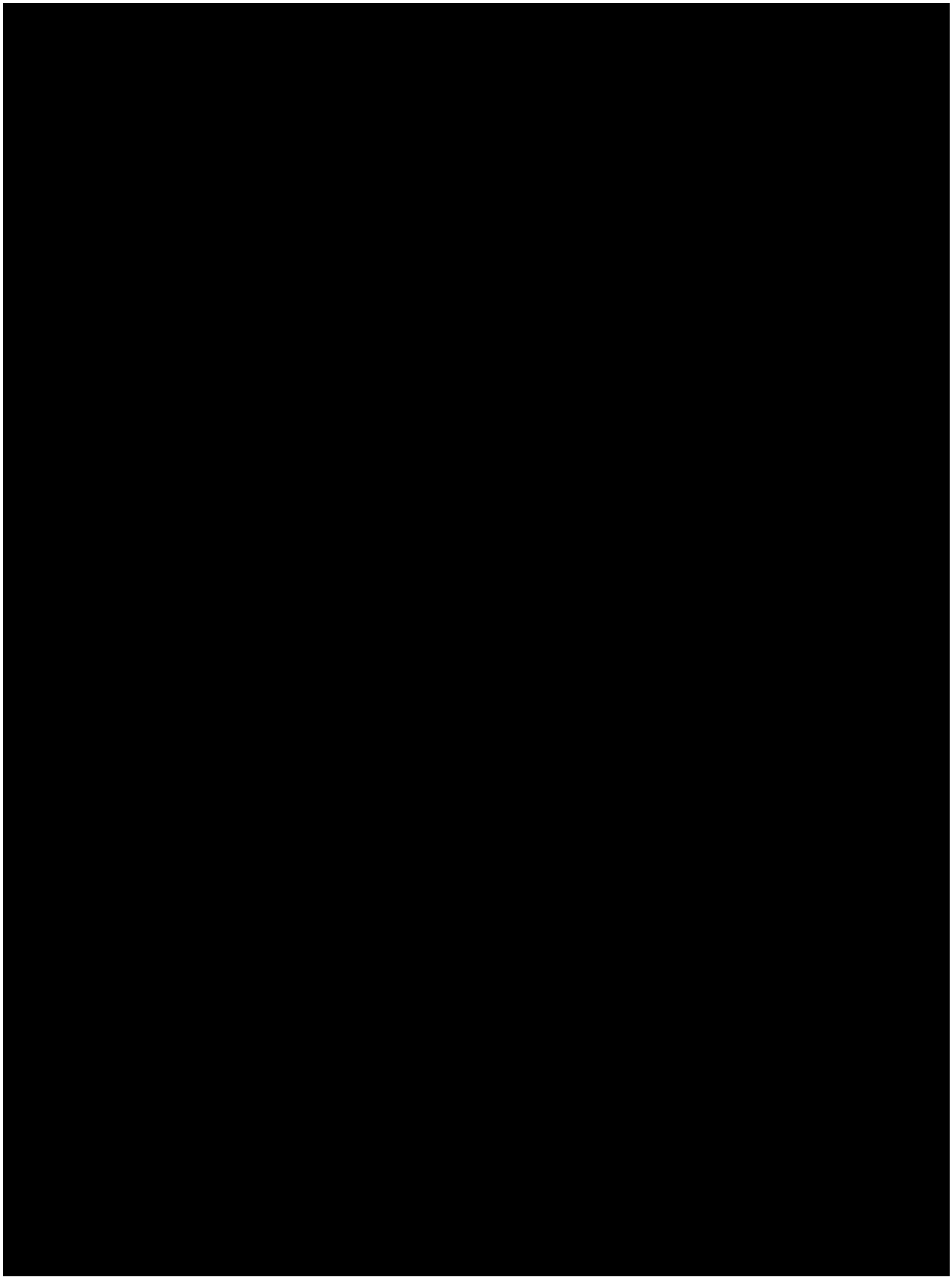
EMA Guidance: 2012 Guideline on the evaluation of anticancer medicinal products in man.

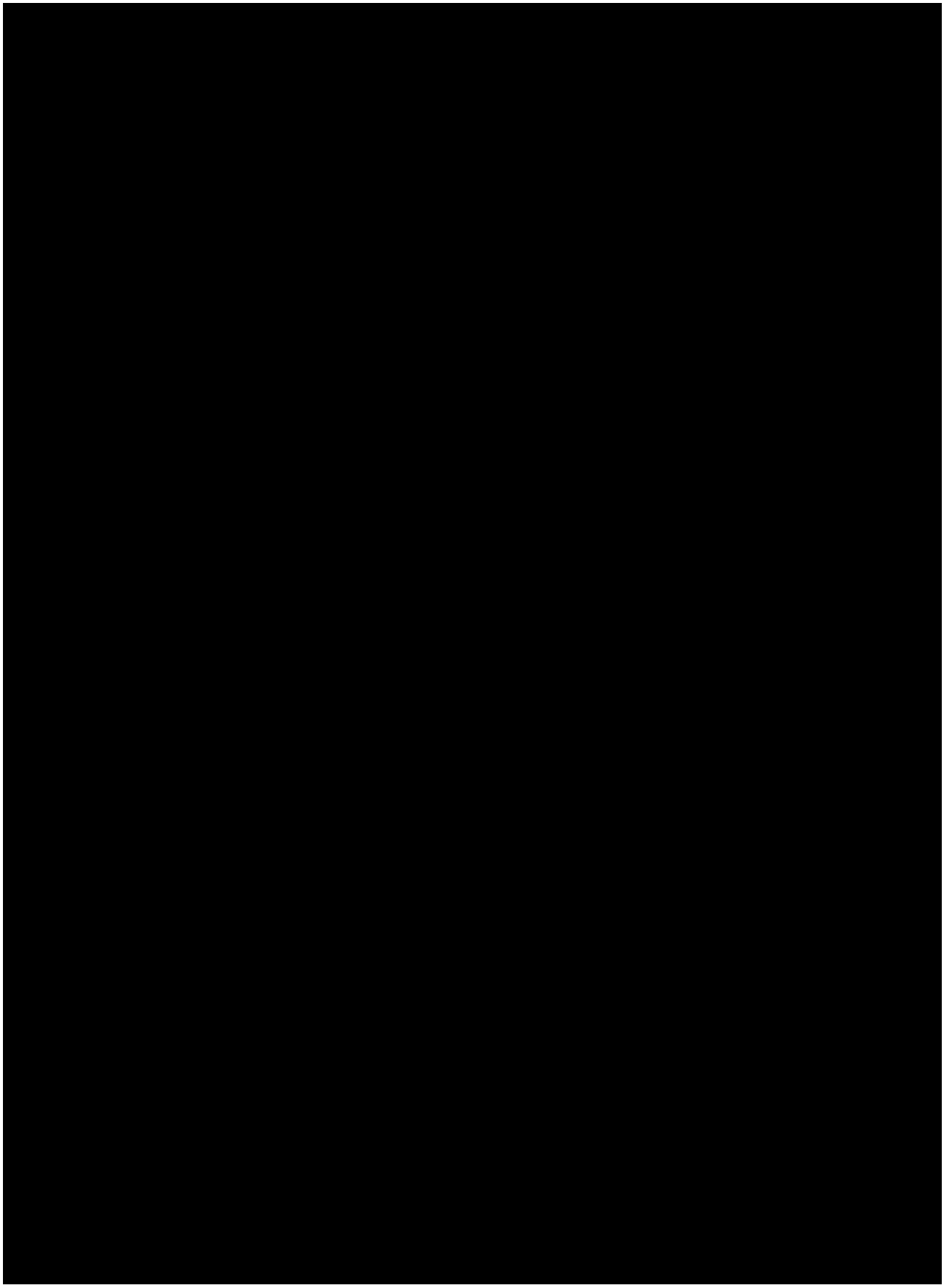
FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

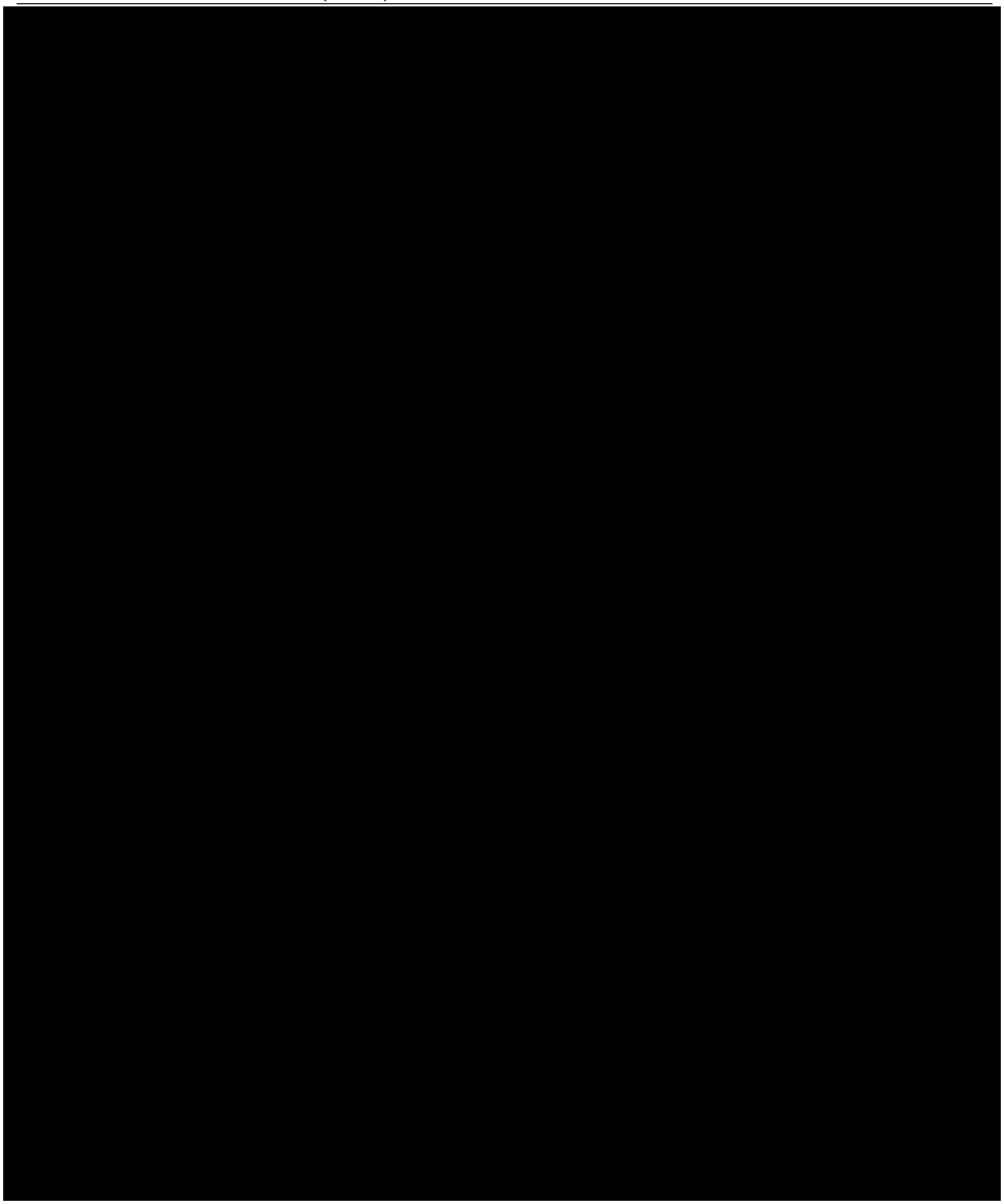
FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9:11-18.

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, J Natl Cancer Inst; 92:205-16.







16.3 Appendix 3: Bayesian model set-up and prior specifications

16.3.1 Statistical model

For each treatment group, the underlying PFS time (in days) will be modeled using a two-piece exponential distribution, which allows the specification of different hazard rates before/after the possible delayed effect. The survival function is given by

$$\mathrm{PFS}(t) = \exp(-\lambda_{i1} * t), \text{ if } t \leq r_i;$$

$$\mathrm{PFS}(t) = \exp(-\lambda_{i1} * r_i) * \exp(-\lambda_{i2} * (t - r_i)), \text{ if } t > r_i$$

Where t is study day, r_i is the risk changing time-point (i.e., the time to the delayed effect), λ_{i1} and $\lambda_{i2}$are the hazard rates before/after the delayed effects and i indicates the treatment group, $i = 1$ for capmatinib plus pembrolizumab and $i = 2$ for pembrolizumab alone. The corresponding HR between capmatinib plus pembrolizumab and pembrolizumab alone after the delayed effects is $\lambda_{12}/\lambda_{22}$.

In a clinical trial, the time to progression may lie between the assessment at which the event is observed and day of the previous assessment+1 when patients have an event of progression. It is assumed the time to the event has a uniform distribution within this period.

16.3.2 Prior specifications

Priors for the risk change-point

Gamma priors are used for the time of the risk change-point, r_i (i=1, 2). For each treatment group the prior is selected such that the mode is 64 days (i.e. three treatment cycles+1 day, the planned time of the first post-baseline tumor assessment) and the variance is 20. The resulting priors for r_i (i=1, 2) are Gamma(206.8, 3.2).

Priors for the first period

A common prior will be assumed for PFS in the first period (i.e., before the delayed effect) for both treatments. Gamma priors are used for λ_{i1} (i=1, 2), selected such that the resulted median PFS rate at Day 64 is around 75% (a rate determined from prior data) and the probability of PFS rate at Day 64 being less than 50% is approximately 0.05. The resulting priors for λ_{i1} are Gamma(2.6, 507.2).

Full prior for capmatinib + pembrolizumab PFS

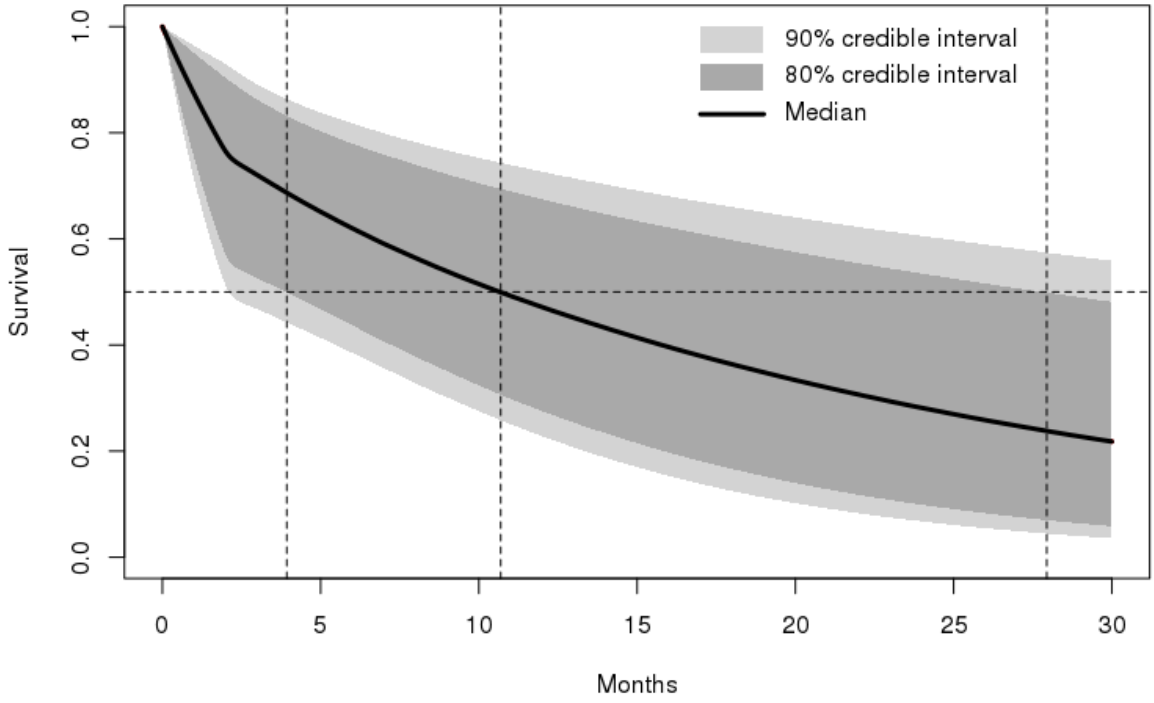
Prior for the second period

A weakly informative gamma prior for λ_{12} is used. The prior is selected such that if the risk change-point is 64 days, and the fraction of patients progression free at this point is 75% that the overall median PFS is approximately 12 months, with wide credible interval. The resulting prior is Gamma(2.6, 1601.1),

Full prior

Combining the priors for r_1, λ_{11}, and λ_{12} gives the complete specification of the prior of PFS for the capmatinib + pembrolizumab arm (Figure 16-1). This is a weakly informative prior with median PFS of 10.7 months and a wide 80% credible interval of (3.9, 27.9) months.

Figure 16-1 Full prior distribution for capmatinib + pembrolizumab PFS



Full prior for pembrolizumab PFS

Priors for the second period

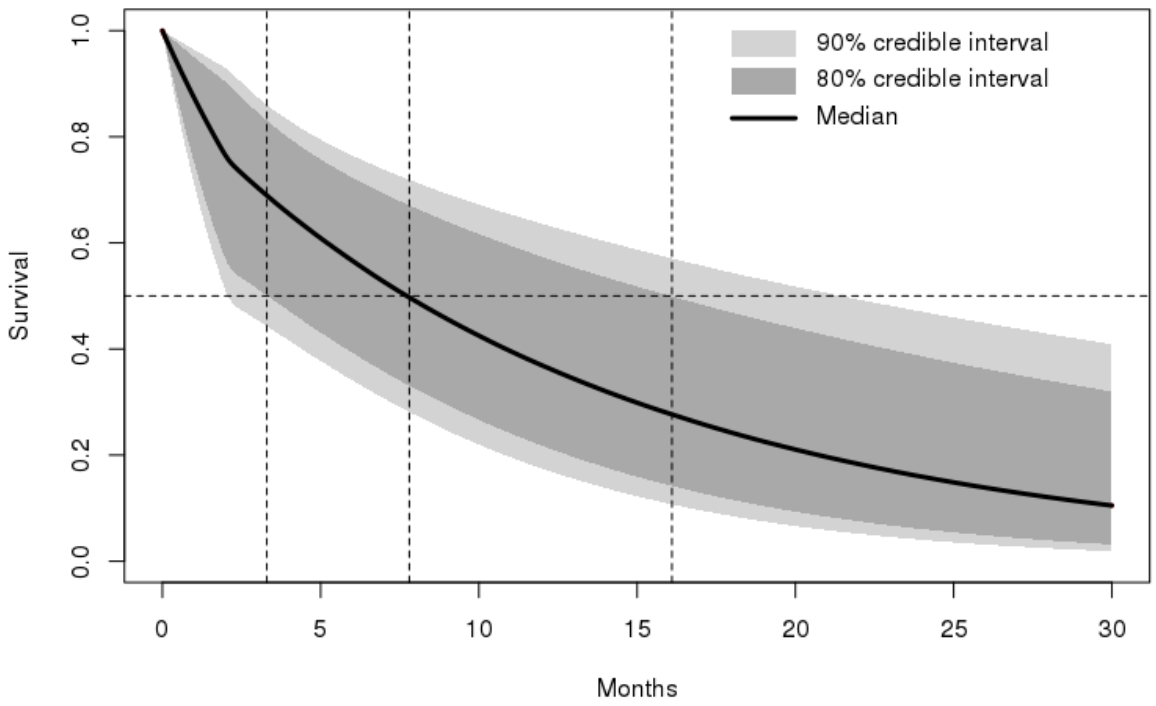
For pembrolizumab alone, a three component mixture of gamma distributions is used for the prior for λ_{22}. These components correspond to PFS as reported in the Keynote 024 trial, PFS as reported in the Keynote 042 trial, and a weakly informative robustification component to represent the case that neither of the prior Keynote trials are representative of PFS as observed on this trial. The prior components to represent the prior Keynote trials were selected such that under the assumption that the risk change-point is 64 days, and that 75% of patients are progression free at this point that the prior median PFS approximates to the reported median PFS, and the lower limit of the 95% credible interval lies below the reported lower limit of the 95% confidence interval for median PFS. The robustification prior component was selected such that it has a median lying approximately midway between the reported median PFSs of the two Keynote trials, with wide credible interval. Weights are assigned to the three components such that the prior Keynote trials are given equal weight, with the robustification component having half of the weight assigned to either component corresponding to a Keynote trial.

The resulting mixture Gamma distribution is: 0.4*Gamma(5.0, 2775.0) + 0.4*Gamma(19.0, 6892.7) + 0.2*Gamma(1.5, 548.8).

Full prior

Combining the priors for r_2, λ_{21}, and λ_{22} gives the complete specification of the prior of PFS for the pembrolizumab arm (Figure 16-2). This is a weakly informative prior with median PFS of 7.8 months and a wide 80% credible interval of (3.3, 16.1) months.

Figure 16-2 Full prior distribution for pembrolizumab PFS



Operating characteristics

The operating characteristics for the Bayesian analysis described in Section 12.4.1.2 are obtained by performing extensive simulations.

16.3.2.1 Generating hypothetical datasets

Let n_i denote the sample size for each treatment group, and a_j denote the accrual rate in the jth accrual month. The values of a_j are specified below:

Month	1st	2nd	3rd	4th	≥5th
Accrual rate	3	6	12	14	15

For each treatment group several possible values for the underlying median PFS are specified. For each scenario with one of the specified value for the underlying median PFS, the hypothetical PFS dataset is generated by the following steps:

1. Set accrual waiting time to 0 for the first patient. Generate accrual waiting times for the remaining patients based on equidistance enrolment within each month with the accrual rate mentioned in the above table, i.e., $1/a_j$ for patients in the jth accrual month.
2. Generate a random sample of n_i PFS times in unit of day following a two-piece exponential distribution with the time-point of risk change as 64 days and the respective risks of progression in the first and second periods of $\lambda_{i1} = -\log(0.75)/64 = 0.0045$ and $\lambda_{i2} = -\log(0.5/0.75)/(1-64)$, corresponding to a PFS function with PFS rate at the time-point of risk change 75% and median PFS of l.

   Take a sample of $n_i \times r_e$ patients from the n_i patients without replacement, where r_e is the early drop-out rate before the first assessment and is pre-specified as 6.25% in this study. Set the corresponding censoring time as 1 day.
3. Generate a random sample of $n_i - n_i * r_e$ censoring times, based on the assumption of an exponential distribution corresponding to a drop-out risk of $r_d = 0.1$ per patient year. Where censoring time is earlier than event time, the patient follow up time is set to the censoring time, and the patient is treated as censored in the subsequent analysis.
4. For each patient an assessment schedule is generated, based on tumor assessments occurring every 9 weeks. A +/- 1 week window is assumed for each assessment, with the timing of the assessment distributed uniformly within this window. For each patient with an event, it is assumed the event is observed at the next assessment on or after the day of the event. For censored patients, the day of censoring is the last assessment on or before the day of censoring.
5. Calculate accrual calendar time (i.e., the cumulative sum of the accrual waiting times before the patient enrolled) and scheduled PFS calendar time (i.e., the sum of accrual calendar time and the event/censoring occurred time time). Rank the non-censored scheduled PFS calendar time from the shortest to the longest. Since the primary analysis will be performed after 50 events are observed, the 50th non-censored scheduled PFS calendar time will be considered as the day of analysis.
6. For patients with progression events after the day of analysis, and hence censored in that analysis, the censoring time is set to be the day of last assessment on or before the day of analysis cut-off.

The steps 1-6 above are repeated to generate a total of 1000 hypothetical datasets for each scenario.

16.3.2.2 Posterior analysis

Given the prior distributions and parameter values specified above, the corresponding posterior distributions for each of the 1000 hypothetical datasets are obtained by performing extensive MCMC simulations using R package R2jags with 5000 iterations plus a burn-in length of 3000 for each of two chains. For each pair of posterior values of λ_{12} and λ_{22}, the HR after the time-point of risk change HR2 is calculated as $\lambda_{12}/\lambda_{22}$. The calculated HR from the iterations form the posterior distribution for the primary endpoint. The mean, median, standard deviation and 90%-quantile will be calculated from this posterior distribution. The operating characteristics in terms of probability of success among 1000 hypothetical datasets for the above mentioned Bayesian study design under different true median PFS for each arm are summarized in the following table.

Table 16-7 Probabilities to declare a success under various scenarios

Scenario (capmatinib plus pembrolizumab vs. pembrolizumab) PFS in months (Hazard ratio)	Sample size and primary analysis timing			
	N=75, when 50 events were observed	N=96, when 50 events were observed	N=96, when 60 events were observed	N=105, when 70 events were observed
7.1 vs. 7.1 months (HR2=1)	0.110	0.110	0.143	0.096
8.5 vs. 8.5 months (HR2=1)	0.135	0.160	0.148	0.158
10.3 vs. 10.3 months (HR2=1)	0.155	0.196	0.189	0.174
12.8 vs. 8.5 months (HR2=0.598)	0.684	0.716	0.700	0.770
12 vs. 7.1 months (HR2=0.505)	0.825	0.850	0.871	0.883
15 vs. 8.5 months (HR2=0.496)	0.834	0.855	0.891	0.909
18.5 vs. 10.3 months (HR2=0.501)	0.856	0.840	0.888	0.914

Note: The success criteria are defined as at least 50% confidence level that HR≤ 0.7 and at least 90% confidence level that HR2<1.

The sample size of 96 patients with the primary analysis timing of 50 events is selected. It is the minimum sample size and minimum number of events that ensures at least 70% probability to declare success if the underlying HR2<0.6, with controlling the probability to declare success under 20% if the underlying HR2=1.

Approval Signatures

Compound:	INC280
Document Title:	CINC280I12201: Protocol v03 - A randomized, open label, multicenter phase II study evaluating the efficacy and safety of capmatinib (INC280) plus pembrolizumab versus pembrolizumab alone as first line treatment for locally advanced or metastatic non-small cell lung cancer with PD-L1# 50%
Document Name:	02.01.0201 Protocol - v03
Document Version:	4.0

Username	User ID	Signing Reason	Date
[redacted]	[redacted]	Content Approval	2021-04-26 01:06:48 (UTC)

Document electronically signed