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INC280 (carpmatinib), PDR001 (spartalizumab)

Clinical Trial Protocol CINC280J12201 / NCT04323436

A double-blind, placebo controlled, randomized, phase II study evaluating the efficacy and safety of capmatinib (INC280) and spartalizumab (PDR001) combination therapy versus capmatinib and placebo as first line treatment for locally advanced or metastatic non-small cell lung cancer patients with MET exon 14 skipping mutations

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List of abbreviations

ADA	Antidrug Antibody
AE	Adverse Event
AESI	AEs of Special Interest
AJCC	American Joint Committee on Cancer
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BID	Bis In Die/twice a day
BIRC	Blinded Independent Review Committee
BLQ	Below the Limit of Quantitation
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
CMV	Cytomegalovirus
CNS	Central Nervous System
CR	Complete Response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CV	Coefficient of Variation
d	Day(s)
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
dl	Deciliter
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DOR	Duration of Response
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-Linked Immunosorbent Assay
EORTC	European Organization for Research and Treatment of Cancer
EOT	End Of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration (US)
FPAS	Full Pharmacokinetic Analysis Set

FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
h	Hour
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCC	Hepatocellular Carcinoma
Hgb	Hemoglobin
HCV	Hepatitis C Virus
[redacted]	[redacted]
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
[redacted]	[redacted]
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IEC	Independent Ethics Committee
IG	Immunogenicity
ILD	Interstitial Lung Disease
IN	Investigator Notification
INR	International Normalized Ratio
IO	Immuno-Oncology
[redacted]	[redacted]
[redacted]	[redacted]
irAE	Immune-related adverse event
IRB	Institutional Review Board
[redacted]	[redacted]
IRT	Interactive Response Technology
[redacted]	[redacted]
[redacted]	[redacted]
iv	intravenous
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit Of Quantification
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
METΔex14	MET exon 14 skipping
min.	Minute(s)

NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
NTI	Narrow Therapeutic Index
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD-1	Programmed cell Death protein 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
[redacted]	[redacted]
PK	Pharmacokinetic(s)
p.o.	Per os/oral(ly)
PR	Partial Response
PRO	Patient Reported Outcome
PS	Performance Status
PT	Prothrombin Time
Q3W	Every three Weeks
Q4W	Every four Weeks
QMS	Quality Management System
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase II dose
R Value	ALT/ALP x ULN
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
SD	Standard Deviation
SOC	Standard Of Care
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
TdP	Torsades de Pointes
TKI	Tyrosine Kinase Inhibitors
TSH	Thyroid Stimulation Hormone
TTR	Time to Response
ULN	Upper Limit of Normal
WoC	Withdrawal of Consent
wt	Wildtype

Glossary of terms

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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., 28 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/ treatment	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)
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
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
Stage of 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 depending on the study design)
Subject number	A unique number assigned to each subject upon signing the informed consent form. 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/group	A treatment arm/group 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 1 (13-Oct-2021)

Amendment rationale

The main purpose of this protocol amendment is to modify the study conduct and data analysis following the sponsor's decision to halt study enrollment on 28-Jul-2021, as communicated to Health Authorities as per local requirements. The enrollment halt decision was based on lack of tolerability observed in capmatinib and spartalizumab combination treatment in the run-in part (Part 1) of the trial.

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

- All ongoing subjects were discontinued from spartalizumab treatment and continue to receive single agent capmatinib, given the proven tolerability and efficacy of capmatinib monotherapy in this study indication.
- Enrolled subjects who had not started study treatment were to receive capmatinib single agent treatment from the start

[redacted]

Due to the change in the study treatment following spartalizumab discontinuation, this study can no longer appropriately assess the clinical activity of the combination. Therefore, data collection requirements will be simplified and the study objectives will be updated, as follows:

- The centralized review of study imaging which was put in place to provide blinded and independent efficacy assessment of the combination treatment is no longer required. [redacted]
- As blinded and independent tumor assessments will no longer be performed, the primary endpoint of the study will be amended to ORR by investigator assessment as per RECIST 1.1, [redacted]. The primary endpoint analysis will be based on the estimation of ORR and hypothesis testing of ORR will not be performed.
- PFS and DCR by investigator assessment will be the study secondary endpoints. PFS will be reported using Kaplan Meier analysis. [redacted]
  The secondary estimand constructed for DOR is no longer applicable.
- In order to capture any potential delayed treatment effect of the combination, BOR and PFS will take into account all available tumor assessments irrespective of spartalizumab discontinuation due to any reason including sponsor decision. The intercurrent events of the primary estimand were updated accordingly.
- [redacted]
- [redacted]

To reduce the assessment burden for trial subjects, the frequency of radiological assessments will be reduced to every 12 weeks after at least 2 post-baseline tumor assessments have been obtained. Tumor assessment follow-up, survival follow-up and information on antineoplastic therapies after study treatment discontinuation will not be collected.

The end of study definition was updated to ensure that subjects, who had received at least one dose of spartalizumab, will complete all required safety assessments up to 150 days from the last dose of spartalizumab treatment and will have at least 2 post-baseline tumor assessments obtained for the purpose of the primary outcome measure, in case another clinical study or an alternative treatment option becomes available to continue capmatinib provision.

This protocol amendment will also incorporate the following changes:

- Based on available data, capmatinib is not expected to have any clinically relevant effect on QTc (capmatinib Investigator's Brochure); drugs with known risk of Torsade de Pointes (TdP) were therefore removed from the list of capmatinib prohibited concomitant medications.
- Since capmatinib monotherapy has proven tolerability and efficacy in this study indication, dose re-escalation of capmatinib after dose reduction will be allowed. The criteria for dose re-escalation of capmatinib was added.
- As all ongoing subjects are treated with single agent capmatinib after spartalizumab discontinuation, dose modification guidance and recommended follow-up for toxicities which specifically apply to capmatinib monotherapy were added. The guidance for follow-up on potential drug-induced liver injury (DILI) cases was also updated.
- To allow flexibility in administering supportive treatment for bone metastasis and cancer-related pain, the protocol was updated to allow limited-field radiotherapy for analgesic purposes or for lytic lesions at risk of fracture. Bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor for pre-existing bone metastases are also now permitted.
- Following the emergence and availability of COVID-19 vaccines worldwide, the protocol language in relation to vaccination conduct during the study was updated to clarify the use of live vaccines.
- The assessment of benefit/risk concluded the absence of additional risks related to COVID-19. To ensure subject safety and trial integrity in the event of public health emergency, mitigation procedures to ensure participant safety were added in relevant sections.

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

Study Update

As of 28-Jul-2021 when enrollment was halted, 28 patients were treated with capmatinib plus spartalizumab and 3 patients were in screening in the run-in part (Part 1) of the study. The patients who were on combination treatment have discontinued spartalizumab and are continuing on capmatinib single agent since the enrollment halt. The patients who were in screening at the time of the enrollment halt have started receiving capmatinib single agent treatment. As of 06-Sep-2021, 19 patients were still on treatment with capmatinib.

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 has been updated according to the changes made in the main text of the protocol
- Section 1.1.1, Overview of capmatinib (INC280): Addition of reference to the approval of capmatinib
- Section 1.1.1.2, Clinical experience: Addition of MATE to the list of transporters inhibited by capmatinib amd addition of results of capmatinib QT analysis
- Table 2-1, Objectives and related endpoints:
  - Primary endpoint (Part 1) was updated to ORR by investigator assessment
  - [redacted]
- Section 2.1, Primary estimand in Part 1 was updated
- Section 2.2, Secondary estimand: in part 1 is no longer applicable
- Section 3, Study design:
  - Addition of footnote indicating spartalizumab treatment discontinuation
  - It was clarified that tumor assessment follow up and survival follow up will not be performed
- Section 3 and Section 4.1, Rationale for study design: Update of primary endpoint to ORR by investigator assessment
- Section 3, Section 4.1 and Section 4.4, Purpose and timing of interim analyses: Removal of information regarding Part 2 initiation
- Section 4.5.3, Capmatinib combined with spartalizumab: Update of the risk benefit following enrollment halt and spartalizumab discontinuation
- Section 4.6: Rationale for public health emergency mitigation procedures was added
- Section 6.1.3, Treatment arms and Section 6.7.2, Instructions for prescribing and taking study treatment: was clarified that following enrollment halt spartalizumab was discontinued
- Section 6.2.1, Concomitant therapy: The use of bisphosphonates or RANKL inhibitor treatment of bone metastases and permitted radiotherapy were clarified
- Section 6.2.1.1, Permitted concomitant therapy: Description of concomitant therapies requiring caution and/or action was aligned with other capmatinib clinical trials. No new class added
- Section 6.2.2, Prohibited medication: The use of palliative radiotherapy and live vaccine was clarified
- Section 6.2.2.1, Capmatinib: prohibited medication: Drugs with known risk of Torsade de Pointes (TdP) have been removed from the list of prohibited concomitant medications for capmatinib, section reworded to align with other capmatinib studies

- Section 6.5.1, Dose modifications:
  - It was clarified that following spartalizumab discontinuation, only capmatinib guidance is applicable
  - Dose modification language for capmatinib monotherapy and language to permit re-escalation of capmatinib was added
- Section 6.5.2, Follow-up for toxicities:
  - It was clarified that for subjects who are transferred to another clinical study or alternative treatment option to continue capmatinib treatment at end of study, no further safety data will be collected as part of this study.
- Table 6-3 was updated with criteria for dose reduction/ interruption and re-initiation and follow-up of toxicities, to align with other capmatinib studies
- Section 6.5.2.1, Follow-up on potential drug-induced liver injury (DILI) cases: Guidance for follow up of DILI cases was aligned with other capmatinib studies
- Section 6.7.1.1 was updated to include language related to destruction of unused study drug at site.
- Section 7, Informed consent procedures and Section 8, Visit schedule and assessments: Addition of mitigation procedures under public health emergency
- Table 8-1b was added with a simplified assessments schedule for Part 1 and replaces Table 8-1
- Section 8.2, Subject demographics/other baseline characteristics: Information for collection of race and ethnicity data was added
- Section 8.3.1, Tumor imaging: It was clarified that frequency of imaging assessments is reduced to every 12 weeks once trial subjects have obtained at least 2 post-baseline tumor assessments. In addition, study imaging will no longer be submitted for central imaging review
- Section 8.3.1.3, Confirmation of disease progression by BIRC is no longer applicable
- Section 8.3.2: Overall survival is no longer applicable
- Section 8.5.1, Patients reported outcomes: Clarification that PROs will no longer be collected
- Section 8.5.2, Pharmacokinetics: Language to allow use of residual PK samples for [redacted] analyses was added and it was clarified that PK and IG sampling for spartalizumab is no longer applicable
- [redacted]
- Section 9.2.1, End of study: Clarification of end of study for subjects who transfer to another clinical study or an alternative treatment option
- Section 9.2.2, Post treatment follow-up: Removal of tumor assessment follow-up and survival follow-up
- Setion 9.2.2.1, Safety follow-up: Removal of 150 day follow up visit, PK and IG and PRO assessments
- Section 10.1.3, SAE reporting: clarification about SAE reporting was added

- Section 10.2.2, Data monitoring committee (DMC): It was clarified that following enrollment halt, the DMC section is no longer applicable
- Section 12, Data analysis and statistical methods:
  - It was clarified that following the study enrollment halt during Part 1, Part 2 will not be initiated
  - Reporting details of CSR was updated
- Section 12.4.1.2, Statistical hypothesis, model, and method of analysis: Hypothesis testing for ORR was removed and clarifed that subjects who had not received one of the investigational drugs at all would be excluded from the efficacy analysis.
- Section 12.4.1.3, Handling of intercurrent events of primary estimand: updating the way to handle intercurrent events for Part 1
- Section 12.4.1.4, Handling of missing values/censoring/discontinuations: it was clarified that subjects without confirmed CR/PR would be considered as non-responders.
- Section 12.5.2.1, Efficacy endpoint(s): Removed ORR, OS, DOR and TTR
- [redacted]
- [redacted]
- Section 12.7, Interim analyses: it was clarified that no formal interim analysis is planned for Part 1 of the study
- Section 13.5 Participant engagement language was included
- Table 16-13, Drugs with known risk of TdP was removed

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

IRBs/IECs

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

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

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

Protocol summary

Protocol number	INC280J12201
Full Title	A double-blind, placebo controlled, randomized, phase II study evaluating the efficacy and safety of capmatinib (INC280) and spartalizumab (PDR001) combination therapy versus capmatinib and placebo as first line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) patients with MET exon 14 skipping (METΔex14) mutations
Brief title	Study of efficacy and safety of capmatinib in combination with spartalizumab in naive patients with EGFR wild type (wt), ALK rearrangement negative advanced NSCLC, harboring METΔex14 mutations.
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy and safety of capmatinib in combination with spartalizumab in treatment naive patients with EGFR wt, ALK rearrangement negative advanced NSCLC, harboring METΔex14 mutations. A run-in part (Part 1) will be conducted to determine the anti-tumor activity and safety of capmatinib in combination with spartalizumab. Upon review of safety data and confirmation of anti-tumor activity in Part 1, the randomized part (Part 2) will be initiated to compare the efficacy and safety of capmatinib plus spartalizumab to capmatinib plus placebo. Combined treatment of METΔex14 mutated NSCLC with capmatinib and spartalizumab is expected to result in improved efficacy compared to each single agent due to direct targeting of an oncogenic driver (MET) as well as more efficient stimulation of an anti-tumor immune response than with PD-1 blockade alone.
Primary Objective(s)	**Run-in part** (Part 1): • To evaluate the anti-tumor activity of capmatinib in combination with spartalizumab as measured by overall response rate (ORR) by investigator assessment according to RECIST 1.1 **Randomized part** (Part 2): • To compare the efficacy of capmatinib plus spartalizumab to capmatinib plus placebo by assessing Progression Free Survival (PFS) by BIRC according to RECIST 1.1

Secondary Objectives	**Run-in part** (Part 1): • To assess safety and tolerability of capmatinib in combination with spartalizumab • To further evaluate the anti-tumor activity of capmatinib in combination with spartalizumab • To evaluate the PK of capmatinib and spartalizumab **Randomized part** (Part 2) • To compare OS of capmatinib in combination with spartalizumab versus capmatinib plus placebo • To assess safety and tolerability of capmatinib in combination with spartalizumab versus capmatinib plus placebo • To further evaluate the anti-tumor activity of capmatinib in combination with spartalizumab versus capmatinib plus placebo • To evaluate patient reported outcomes of capmatinib in combination with spartalizumab versus capmatinib plus placebo • To evaluate the PK of capmatinib and spartalizumab • [redacted]
Study design	This study consists of two parts: • A single arm run-in part of capmatinib in combination with spartalizumab (Part 1). • A randomized double-blind placebo controlled part (Part 2) of capmatinib in combination with spartalizumab versus capmatinib plus placebo (randomization ratio 2:1). Randomization will be stratified by presence or absence of brain metastasis at baseline (as assessed by investigator per RECIST 1.1) and PD-L1 expression (<1%, 1-49%, ≥50%). Treatment cross-over is not allowed. Following the study enrollment halt during Part 1, Part 2 will not be initiated.
Population	This study will include adult male and female patients with stage IIIB, IIIC or IV NSCLC harboring METΔex14 mutations, who have not received prior systemic therapy for advanced/metastatic disease. Approximately 270 subjects will be treated in the study: ca. 30 in Part 1 and ca. 240 randomized in Part 2.
Key Inclusion criteria	• Histologically confirmed locally advanced or metastatic NSCLC which is EGFR wt, ALK rearrangement negative and METΔex14 mutated • No prior systemic therapy for advanced/metastatic disease (neo-adjuvant/adjuvant treatment completed > 12 months before relapse are permitted) • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 • Measurable disease as per RECIST 1.1 • Known PD-L1 tumor expression status (applicable to Part 2 only)
Key Exclusion criteria	• Prior treatment with a PD-1/PD-L1 inhibitor, MET inhibitor or HGF inhibitor • Presence of symptomatic CNS metastases or requiring local CNS-directed therapy (radiotherapy or surgery), or increasing doses of corticosteroids 2 weeks prior to study entry

	• Impaired cardiac function or clinically significant cardiac disease • Presence or history of interstitial lung disease, non-infectious pneumonitis or interstitial pneumonitis, including clinically significant radiation pneumonitis • History of allogenic bone marrow or solid organ transplant • Radiotherapy to lung fields ≤ 4 weeks or to any other anatomic site ≤ 2 weeks prior to start of study treatment (palliative radiotherapy for bone lesions is allowed)
Study treatment	**Run-in part** (Part 1): • Capmatinib 400 mg p.o. BID plus spartalizumab 400 mg iv Q4W **Randomized part** (Part 2): • Arm 1: capmatinib 400 mg p.o. BID plus spartalizumab 400 mg iv Q4W • Arm 2: capmatinib 400 mg p.o. BID plus spartalizumab matching placebo iv Q4W A complete cycle of treatment is defined as 28 days of continuous capmatinib treatment and an infusion of spartalizumab or placebo every 28 days.
Efficacy assessments	• Radiological tumor assessment by investigator assessment as per RECIST 1.1 at screening and every 8 weeks, then every 12 weeks when at least 2 post-baseline radiological tumor assessments have been performed.
Pharmacokinetic assessments	• Concentrations and derived PK parameters of capmatinib and spartalizumab • Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on treatment with spartalizumab
Key safety assessments	• Physical examination • ECOG performance status • Vital signs • Performance status • Laboratory assessments, including hematology, chemistry, thyroid function and coagulation • 12-lead ECGs • Monthly pregnancy testing for women of child-bearing potential • Adverse events (AEs), the severity, the relationship to study treatment and the seriousness
[redacted]	[redacted]
Data analysis	**Run-in part (Part 1)** The primary objective is to evaluate the anti-tumor activity of capmatinib in combination with spartalizumab, as measured by ORR by investigator assessment according to RECIST 1.1. Participants who did not receive one of the investigational drugs at all will be excluded from the efficacy analysis. No formal interim analysis is planned.. **Randomized part (Part 2)**

	Following the study enrollment halt, Part 2 will not be initiated. The primary objective is to evaluate whether spartalizumab in addition to capmatinib prolongs PFS by BIRC according to RECIST 1.1 compared to capmatinib plus placebo. The following null and alternative hypothesis will be tested to address the primary efficacy objective: $H_{01}: \theta_1 \geq 1$ vs $H_{11}: \theta_1 < 1$ Where θ_1 is the PFS hazard ratio (HR) (capmatinib in combination with spartalizumab versus capmatinib plus placebo). The primary efficacy analysis to test these hypotheses and compare the two treatment groups will be based on a stratified log-rank test at an overall one-sided 2.5% significance level. The stratification will be based on the stratification factors assigned at randomization (i.e. presence or absence of brain metastasis at baseline and PD-L1 expression [<1%,or 1-49%, or ≥50%]). Analysis will be based on the Full Analysis Set (FAS) population according to the randomized treatment group and strata assigned at randomization. The PFS analysis will be performed as a part of a two-look group sequential design using a Lan-DeMets alpha spending function with O'Brien-Fleming type stopping boundary to control the type I error probability. The primary intent of this interim analyses is to report early outstanding efficacy results in terms of PFS. The interim analysis for PFS is planned after approximately 145 PFS events (i.e. at approximately 75% information fraction) have been documented. PFS will be summarized using the Kaplan-Meier (KM) method. Median PFS, with corresponding 95% CI, and 25th and 75th percentiles will be presented by treatment group. The hazard ratio for PFS will be estimated, along with its 95% confidence interval, using a stratified Cox proportional hazard model using the same stratification factors as for the log-rank test. The key secondary objective is to evaluate whether spartalizumab when added to capmatinib prolongs OS compared to capmatinib plus placebo. A hierarchical testing procedure will be adopted and the statistical test for OS will be performed only if the primary efficacy endpoint PFS is statistically significant. A similar hypothesis and model will be used to address the key secondary efficacy endpoint for OS. A maximum of four analyses are planned for OS. The OS analysis will be performed as a part of a four-look group sequential design using a Lan-DeMets alpha spending function with O'Brien-Fleming type stopping boundary to control the type 1 error probability. At the time of the interim and primary PFS analysis, interim OS analyses for a possible early significance claim will be performed. An additional interim OS analysis will be performed when approximately 167 deaths (85% of the deaths) have been observed, in case the time gap between the final analysis for PFS and for OS is longer than 1 year. A final OS analysis will be performed when approximately 197 deaths have been observed. A hierarchical testing approach will be used to control the overall type I error, where OS will only be formally tested and interpreted if the primary analysis for PFS is statistically significant. If PFS is not

	statistically significant at either the interim PFS analysis or final PFS analysis, the third interim OS analysis and final OS analysis will not be performed. Additional details on the interim analyses for PFS and OS are provided in Section 12.7. Refer to Section 12.4.1 and Section 12.5.1 for details on censoring, intercurrent events, as well as sensitivity and supplementary analyses that will be performed for the primary and key secondary efficacy endpoints.
Key words	INC280, PDR001, capmatinib, spartalizumab, NSCLC, EGFR wt, ALK rearrangement negative, MET inhibitor, MET exon 14 skipping mutation

1 Introduction

1.1 Background

Lung cancer is the most common cancer type worldwide, with an estimated 2.1 million new cases worldwide in 2018, representing 11.6% of all new cancers. It is also the most common cause of death from cancer, with 1.8 million deaths representing 18.4% of the total deaths from cancer (Bray et al 2018). In 2019, approximately 142,670 deaths due to lung cancer are expected in the United States (US) (Siegel et al 2019) and 280,000 in the European Union (Malvezzi et al 2019).

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases. MET mutations leading to exon 14 skipping have been reported in approximately 2% to 4% of the NSCLC population (TCGA 2014, Frampton et al 2015, Paik et al 2015, Awad 2016, Campbell et al 2016, Schrock et al 2016, Tong et al 2016, Lu et al 2017, Benayed at al 2019).

Activating mutations in EGFR and ALK translocations are molecular drivers in NSCLC and their presence is strongly predictive of superior response to EGFR and ALK Tyrosine Kinase Inhibitors (TKIs) when compared to standard chemotherapy. For subjects harboring EGFR activating mutations and ALK translocations, targeted therapies have become the standard of care in both treatment-naive and pretreated patients (Ettinger et al 2010, Zhou et al 2011, Fukuoka et al 2011, Rosell et al 2012, Sequist et al 2013, Shaw and Engelman 2013, Shaw et al 2013, Solomon et al 2014, NCCN 2018). The success of EGFR and ALK TKIs highlights the importance of identifying specific molecular drivers of NSCLC and appropriately direct targeted agents to specific patient populations. Similarly, other TKIs directed at rare targets like ROS1 translocations and BRAF V600 mutations are now available for subsets of patients harboring these oncogenic drivers. (Solomon et al 2014, Hamanishi et al 2016). The potential for prolonged and meaningful clinical response, by targeting these oncogenic drivers, delays the need for chemotherapy or other treatments.

Current treatment options for advanced NSCLC patients are systemic chemotherapy and Immuno-Oncology (IO) therapy (Gettinger and Lynch 2011, Hirsch et al 2016, Morgensztern and Herbst 2016, Reck et al 2016), unless a patient has a "druggable molecular driver" and hence is a candidate for targeted therapy (NCCN 2019). Compared to systemic chemotherapy, targeted therapies are associated with improved progression-free survival (PFS) and quality of life (QoL) in patients with advanced NSCLC (Solomon et al 2014, Yang et al 2016, Brahmer et al 2017, Hida et al 2017, Reck 2018).

Treatment options for patients with advanced NSCLC with no established molecular driver (e.g. ALK gene rearrangements, ROS1 rearrangements, sensitizing EGFR mutations and BRAF V600E point mutations) are based on IO, either as monotherapy or in combination with platinum doublets (Planchard et al 2018, NCCN 2019). Single-agent IO treatment is considered as first-line treatment in patients whose tumors have programmed death-ligand 1 (PD-L1) expression > 50%, and in pretreated patients irrespective of PD-L1 expression (Planchard et al 2018, NCCN 2019). The programmed cell death protein 1 (PD-1) inhibitor pembrolizumab is also approved by FDA as monotherapy for first-line treatment of advanced NSCLC whose tumors express PD-L1 (tumor proportion score (TPS) ≥ 1%). A combination of IO treatment with platinum doublets may be considered as first-line treatment irrespective of tumor PD-L1

expression (Garon et al 2015, Reck et al 2016, Gandhi et al 2018, Hellmann et al 2018, Paz-Ares et al 2018, Sheela et al 2018, Socinski et al 2018, Heinhuis et al 2019). Alternatively, systemic chemotherapy without the addition of IO treatment is an option for patients not eligible for single agent or combination IO therapy (Fossella et al 2000, Schiller et al 2002, Lilenbaum et al 2005, Pujol et al 2005, Scagliotti et al 2008, Scagliotti et al 2014, Malhotra et al 2017).

Outcomes of treatment with platinum-doublet chemotherapy remain poor for locally advanced/metastatic NSCLC in the treatment-naive setting, with a median PFS of 5-7 months and OS of 10-16 months (Scagliotti et al 2008, Ciuleanu et al 2009, Ettinger et al 2010, Paz-Ares et al 2012).

Patients with NSCLC tumors harboring molecular drivers have limited benefit from IO treatments as single agent or in combination with chemotherapy and and should receive IO-based therapies only after exhausting the benefit from the appropriate targeted therapy (Mazieres et al 2019).

In human cancer, the MET pathway is frequently dysregulated, triggering a diverse set of signaling cascades (including the RAS-MAPK as well as the PI3K-AKT pathway), which promote proliferation, survival, motility and angiogenesis of tumor cells (Christensen et al 2005). Several mechanisms have been identified through which the MET pathway becomes aberrantly activated in cancer, including MET exon 14 skipping (METΔex14) mutations, MET gene amplification, chromosomal rearrangements leading to MET fusion proteins, MET receptor overexpression, and autocrine or paracrine activation of MET by its ligand HGF. METΔex14 mutations and MET amplification are currently the most studied MET dysregulations in NSCLC, being evaluated as predictors of response to MET inhibitors.

The presence of METΔex14 mutations lead to loss of the juxtamembrane domain of the receptor, which causes protein stabilization and oncogenic activation (Kong-Beltran et al 2006). Next generation sequencing of tumor specimens has identified many different variants resulting in exon 14 skipping. These variants are rare and collectively found at a frequency of 2-4% in lung cancer (Frampton et al 2015, Schrock et al 2016). Recent clinical observations suggest that such mutations are predictors of response to capmatinib and other MET targeting agents (Frampton et al 2015, Paik et al 2015, Jenkins et al 2015, Mendenhall and Goldman 2015, Waqar et al 2015, Liu et al 2015, Schuler et al 2016, Drilon 2016, Cedres et al 2018, Wolf et al 2018).

In NSCLC, MET dysregulation has been found to be a negative prognostic factor (Guo et al 2014, Landi et al 2017, Awad et al 2019), particularly when both MET amplification and mutation occur in the same tumor (Awad et al 2019).

Currently, there is no approved targeted therapy for patients with METΔex14 mutated NSCLC tumors. Treatment options are limited, because MET mutations are known to be mutually exclusive of other established oncogenic molecular drivers in NSCLC and mostly occur in elderly patients (more than two-thirds > 65 years, Schrock et al 2016), in whom triplet combinations of platinum doublet and IO treatment may often not be feasible due to poor tolerability compared to younger patients with less comorbidities.

To date, data on the efficacy of IO therapies in MET mutated NSCLC are limited and mostly based on retrospective analyses for anti-PD1 single agent treatment. These indicate a moderate benefit from IO therapy irrespective of the line of therapy with Overall Response Rates (ORR) 6-20% and median PFS below 2 months, without significantly improved efficacy in tumors with PD-L1 expression ≥ 50% or high tumor mutation burden (TMB) (Sabari et al 2017, Sabari et al 2018, Awad et al 2019, Baba et al 2019, Mazieres et al 2019).

There have been promising efficacy data in clinical studies with MET inhibitors, including capmatinib, in patients whose tumors harbor METΔex14 mutations , confirming the value of this class of mutations in predicting the response to targeted therapies directed against MET (Frampton et al 2015, Jenkins et al 2015, Mendenhall and Goldman 2015, Paik et al 2015, Waqar et al 2015, Drilon 2016, Liu et al 2016, Schuler et al 2016, Wolf et al 2017, Wolf et al 2018, Wolf et al 2019).

The combination of targeted and IO therapies may represent an opportunity to improve outcome for METΔex14 mutated NSCLC. The rationale for such a combination is two-fold: while targeted therapy against a molecular driver yields rapid responses in a high percentage of patients, IO therapy can lead to durable clinical benefit. Therefore, combining targeted and IO therapies may have the potential to result in deep and durable responses in many patients. Emerging data from the COMBI-i trial in BRAF-mutant melanoma, where the kinase inhibitors dabrafenib and trametinib are combined with the anti-PD-1 antibody spartalizumab, appear to support this concept (Long et al 2019).

Besides the role of MET as an oncogenic driver, preclinical studies suggest that MET and its ligand hepatocyte growth factor (HGF) have important functions in immune cells, with MET activity leading to immunosuppression (Molnarfi et al 2015). Several mechanisms of MET/HGF-mediated immune suppression have been proposed. HGF was found to attract immunosuppressive MET-positive neutrophils to tumor and draining lymph nodes, and inhibition of MET by capmatinib was shown to prevent this (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 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 direct actions on immune cells, irrespective of MET dysregulation in the tumor and suggest that MET inhibitors may restore immune cell function.

Clinical observations further support the hypothesis that HGF-mediated MET activation is immunosuppressive: in melanoma patients treated with anti-PD-1 antibodies, an increase of serum HGF during treatment was seen in a subset of non-responders, but not in responders (Glodde et al 2017), indicative of an HGF-mediated immunosuppressive feedback loop similar to that observed in mouse models. Likewise, another study found that high baseline levels of serum HGF were associated with worse clinical outcomes of anti-PD-1 treatment in melanoma (Kubo et al 2019).

In summary, targeting METΔex14 mutated NSCLC with a MET inhibitor (such as capmatinib) and an IO therapy (such as spartalizumab) may lead to deep and durable responses in a high percentage of patients based on multiple complementary mechanisms.

1.1.1 Overview of capmatinib (INC280)

Capmatinib (INC280) is a small adenosine triphosphate (ATP) competitive, orally bioavailable, highly potent, and selective reversible inhibitor of the MET receptor tyrosine kinase (Liu et al 2011, Baltschukat et al 2019). In preclinical studies, capmatinib treatment induced tumor regression in cancer models with METΔex14 mutations, MET amplification, MET overexpression, or HGF-mediated autocrine MET activation. Addition of capmatinib to anti-PD-1 or other IO treatments led to enhanced anti-tumor efficacy in multiple syngeneic mouse models, none of which exhibited any tumor biomarkers of MET dysregulation (Glodde et al 2017 and RD-2017-00370). Efficacy of capmatinib monotherapy in patients with advanced or metastatic NSCLC harboring METΔex14 mutations has been demonstrated in the ongoing pivotal study CINC280A2201 (Wolf et al 2019, see also Section 1.1.1.2). Based on these data, capmatinib received approval for the treatment of treatment-naive and pretreated NSCLC patients with METΔex14 mutations regardless of line of treatment from the US Food and Drug Administration (FDA) and from the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. FDA and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan also granted an orphan drug designation to capmatinib for treatment of patients with MET dysregulated NSCLC.

1.1.1.1 Non-clinical experience

Capmatinib has potent inhibitory activity against the MET kinase *in vitro* [inhibitory concentration (IC)50 = 0.13 ± 0.05 nM in a biochemical assay], and is highly specific for MET with approximately 1,000-fold or greater selectivity over more than 400 other human kinases or mutant variants thereof (Baltschukat et al 2019). Potent inhibitory activity has also been observed in cell-based assays that measure MET-mediated signal transduction, as well as MET-dependent cell proliferation, survival, and migration.

Preclinical data support the use of capmatinib as single agent in NSCLC, gastric cancer, hepatocellular carcinoma, and glioblastoma. MET dependency in preclinical models from these cancer types was either due to strong MET overexpression (mostly as a consequence of gene amplification, observed in lung, gastric or hepatocellular carcinoma), or MET mutations leading to exon 14 skipping (lung cancer), or HGF secretion resulting in an autocrine loop (glioblastoma). In such MET-dependent mouse tumor models, oral dosing of capmatinib led to a block of MET phosphorylation, dose-dependent antitumor activity, and tumor regression at well-tolerated doses (Liu et al 2011, Baltschukat et al 2019). Studies in a MET / HGF co-expressing mechanistic model indicated that plasma levels of capmatinib correlate with both the dose administered and the extent of tumor growth inhibition *in vivo*, and that optimal anti-tumor activity is associated with an exposure that achieves >90% of MET inhibition over the entire dosing interval (Liu et al 2011).

Collectively, the data suggest that capmatinib possesses potent *in vitro* and *in vivo* biological and pharmacologic activities, and further support its clinical development as a potentially effective oral treatment for human cancers with MET dysregulation.

For further details, please refer to the [capmatinib Investigator's Brochure].

1.1.1.2 Clinical experience

Capmatinib has been extensively tested in both cancer and non-cancer subjects. As of the safety cut-off date of 27-Sep-2019, more than 780 subjects with solid tumors have been treated with capmatinib as a single agent, and more than 690 subjects have received capmatinib in combination with other therapies. The recommended phase II dose (RP2D) for capmatinib as a single agent has been determined to be 400 mg BID in tablet formulation.

The most frequent AEs suspected to be related to capmatinib of any grade reported in study CINC280A2201, reference study for the safety profile of capmatinib monotherapy (n=334), across study cohorts and irrespective of MET mutational status, were edema peripheral (41.6%), nausea (33.2%), blood creatinine increased (19.5%), vomiting (18.9%), fatigue (13.8%), decreased appetite (12.6% and diarrhea (11.4%), and the majority were Grade 1/2. The Grade 3/4 AEs suspected to be related to capmatinib in the CINC280A2201 study included edema peripheral (7.5%) and lipase increased (5.1%), alanine aminotransferase increased (4.8%), amylase increased (3.0%), fatigue (3.0%), aspartate aminotransferase increased (2.4%), nausea and vomiting (1.8%), decreased appetite (0.9%), constipation (0.6%), and diarrhea (0.3%).

In the global, prospective, multi-cohort, single arm, open label Phase II study CINC280A2201 single agent capmatinib was evaluated in 97 subjects with METΔex14 mutated advanced NSCLC including 28 treatment-naive (first-line), and 69 pretreated (2nd/3rd line) subjects. The primary analysis demonstrated clinical benefit irrespective of the line of treatment. In first line, ORR was 67.9% (95% CI: 47.6, 84.1), with confirmed Complete Response (CR) in 1 (3.6%) subject and Partial Response (PR) in 18 subjects (64.3%). The median Duration of Response (DOR) was 11.14 months (95% CI: 5.55, NE). Among the 19 responders, 13 subjects (68.4%) had responses that were maintained for ≥ 6 months and for 7 subjects (36.8%) responses were maintained for ≥ 12 months. The Kaplan-Meier estimated event-free rate was 73.0% (95% CI: 46.7, 87.8) at 6 months and 47.3% (95% CI: 22.6, 68.6) at 12 months. The median PFS was 9.69 months (95% CI: 5.52, 13.86) with estimated PFS rates at 6 and 12 months of 70.4% (95% CI: 49.4 83.9) and 49.7% (95% CI: 29.3, 67.1), respectively. Preliminary evidence of intracranial activity was seen in pretreated and in treatment naive subjects (Anon 2019, Wolf et al 2019).

Pharmacokinetics (PK) data collected in clinical trials showed that capmatinib was rapidly absorbed after oral administration with a median time to reach maximum drug concentration (Tmax) ranging from 1 to 2 hours for tablets. The terminal 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 and BCRP transporters. Substrates of CYP1A2, P-gp, and/or BCRP should be avoided in instances where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, the dosage of CYP1A2 substrates, P-gp substrates, or BCRP substrates should be decreased in accordance with the approved prescribing information. In vitro, capmatinib inhibits renal transporter MATE1 and MATE2K with a Ki of 0.28 μM. Coadministration of capmatinib may increase the exposure of MATE1 and MATE2K substrates.

When co-administered with the strong CYP3A4 inhibitor itraconazole, capmatinib AUC increased by approximately 42% without any change in Cmax. When co-administered with the strong CYP3A4 inducer rifampicin, capmatinib AUC and Cmax decreased by 67% and 56%, respectively (CINC280A2102). Hence, strong CYP3A4 inhibitors are to be used with caution and strong CYP3A4 inducers are prohibited in subjects treated with capmatinib.

Capmatinib did not prolong the QT interval to any clinically relevant extent. Following a dose of 400 mg twice daily in clinical studies, no participant had a post-baseline QTcF interval value greater than 500 msec. A concentration-QT analysis showed that the estimated mean QTcF increase from baseline was 1.33 msec with upper bound 90% confidence interval (CI) of 2.58 msec at the mean steady-state Cmax following 400 mg twice daily dosing.

For further details, please refer to the latest version of the capmatinib Investigator's Brochure.

1.1.2 Overview of spartalizumab (PDR001)

Spartalizumab (PDR001) is a monoclonal antibody (mAb) directed against human PD-1. PD-1 is a critical immune-checkpoint receptor that is expressed on CD4 and CD8 T cells upon activation (Freeman 2008). Engagement of PD-1 by its ligands, PD-L1 and PD-L2, transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function (Riley 2009). During tumorigenesis, cancer cells from a wide range of tumor types exploit immune checkpoint pathways, such as PD-1/PD-L1, to avoid detection by the adaptive immune system (Murphy 2011). Inhibitors of immunological checkpoints, including PD-1 and PD-L1 mAbs, have demonstrated significant antitumor activity in patients with various solid tumors.

For further details please refer to the latest [spartalizumab Investigator's Brochure].

1.1.2.1 Non-clinical experience

Spartalizumab is a high-affinity, ligand-blocking, humanized immunoglobulin G4 (IgG4) antibody directed against PD-1 that blocks the binding of PD-L1 and PD-L2, and enhances interleukin-2 production in ex-vivo lymphocyte stimulation assays. It does not cross-react with rodent PD-1; therefore, toxicology studies were performed only in cynomolgus monkeys where there was acceptable cross-reactivity with monkey PD-1. Repeated administration of spartalizumab to monkeys was tolerated at all doses tested up to 100 mg/kg/week for 5 weeks in the GLP toxicology single-agent study. No test article-related in-life, mortality, organ weight changes, or macroscopic findings were noted. There were no spartalizumab-related effects seen in any of the safety pharmacology endpoints assessed (cardiovascular, neurobehavioral, and respiratory). Macrophage infiltrates into the splenic white pulp were observed in animals given

100 mg/kg/week and mononuclear cell infiltrates, often associated with fibrosis, around the injection site blood vessel (saphenous vein) in a few animals given ≥25 mg/kg/week. These spartalizumab-related microscopic changes were fully reversible after an eight week recovery. Additionally, mostly low grade mononuclear infiltrates in the vascular and perivascular space in several tissues of main and recovery treated animals and in recovery controls were observed but with a slightly higher incidence in treated animals. No evidence of parenchymal damage was associated with the vascular/perivascular changes in any of the organs examined and the changes were not associated with any frank tissue injury. Dose-proportional exposure to spartalizumab in each dose group was confirmed. Anti-drug antibodies (ADA) to spartalizumab were observed in some spartalizumab treated cynomolgus monkeys. A trend of reduced drug exposure was observed in these ADA-positive animals. Based on the toxicology studies with spartalizumab as a single-agent, the Highest Non-Severely Toxic Dose (HNSTD) dose is 100 mg/kg.

For further details, please refer to the latest spartalizumab Investigator's Brochure, as well as Section 4.5.1 (Risks and Benefits) and Section 6.5 (Dose Modification) of the protocol.

1.1.2.2 Clinical experience

To date, more than 1200 patients across 23 Novartis sponsored clinical studies have been treated with spartalizumab. Of these, more than 500 patients were exposed to spartalizumab single agent.

The available safety data from these clinical studies indicate that spartalizumab is generally well tolerated. In the dose escalation phase of the first-in-man study CPDR001X2101 in patients with advanced solid tumors, no Dose Limiting Toxicities were reported. The preliminarily identified safety risks associated with spartalizumab are consistent with and characteristic of agents that inhibit the PD-1 receptor, and an advanced cancer population investigated in the respective trials. Severe immune-related adverse events (irAEs) were infrequent and typically manageable with dose interruption and use of immunosuppressive treatment or other supportive therapy as clinically indicated; discontinuations due to irAEs were rare.

In study CPDR001X2101, spartalizumab single-agent was administered as an intravenous infusion over 30 minutes at doses ranging from 1 to 10 mg/kg on an every 2 weeks (Q2W) schedule or at 3 and 5 mg/kg every 4 weeks (Q4W) schedules. Approximately dose-proportional increase in exposure (C1D1 AUC0-336) was observed with doses from 1 to 10 mg/kg and no DLTs were observed. Accumulation of approximately 2.1-3.4-fold was observed with Q2W dosing and 1.6-2.2-fold with Q4W dosing. Population PK analysis indicated that weight-adjusted or flat dosing lead to similar exposure range Therefore, a flat dosing scheme was selected which has the added advantage of convenience and less risk for medication errors. Two recommended phase II dosing regimens have been established: 300 mg Q3W and 400 mg Q4W flat dosing schedules. A flat dose of 400 mg Q4W or 300 mg Q3W is expected to achieve a mean steady-state Ctrough value higher than the ex vivo EC50 for antigen-stimulated IL-2 production, a translational biomarker for PD-1 blockade (Patnaik et al 2015). Based on the safety profile observed in study CPDR001X2101 and the expected Ctrough values, 400 mg Q4W is expected to be a safe and efficacious dose. Based on the available PK and safety data, the recommended phase 2 dose (RP2D) of spartalizumab has been declared as 400 mg i.v. Q4W or 300 mg i.v. Q3W for combination treatment regimens.

Based on pooled safety data from four studies comprising 513 patients treated with single agent spartalizumab across different regimen (400 mg Q4W [n=382], 300 mg Q3W [n=59] and 1-10 mg/kg Q2W or Q4w [n=76]) and various advanced solid tumors types (i.e. mainly non-small cell lung cancer (NSCLC), melanoma, triple negative breast cancer (TNBC), anaplastic thyroid carcinoma, neuroendocrine tumors and nasopharyngeal carcinoma), the most common AEs (>10%), all grades, regardless of relationship with study treatment included: fatigue (23.6%), decreased appetite (19.7%), anemia (19.1%), nausea (19.1%), dyspnea (18.9%), cough (17.2%), pyrexia (16.0%), constipation (15.4%), diarrhea (13.8%), vomiting (12.9%), asthenia (11.5%) and abdominal pain (11.3%). Most common AEs (>3%), all grades, suspected to be study drug related included fatigue (13.1%), hypothyroidism (6.4%), nausea (6.2%), decreased appetitive (5.8%), diarrhea (5.7%), rash (5.5%), pruritus (4.9%), pyrexia (4.7%), asthenia (4.3%), anemia (3.7%), AST increase (3.5%) and ALT increase (3.1%).

Most common SAEs (>1%), all grades, regardless of relationship with study treatment were dyspnea (3.5%), pleural effusion (2.5%), abdominal pain (2.3%), pneumonia (2.3%), pyrexia (1.8%), hypercalcemia (1.6%), anemia (1.4%), sepsis (1.4%) and vomiting (1.2%); there were no SAEs suspected to be study drug related that occurred in more than 1% of patients.

AEs of special interest (AESI) for spartalizumab include endocrinopathies, colitis, skin reactions, hepatitis, nephritis, pneumonitis and other immune-related AEs (irAEs), and infusion reactions.

For further details, please refer to the latest version of the spartalizumab Investigator's Brochure as well as Section 4.5.2 (Risks and Benefits) and Section 6.5 (Dose Modifications) of the protocol.

1.1.3 Overview of combination therapy

1.1.3.1 Non-clinical experience

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 anti-tumor immunity when combined with anti-PD-1 or other IO regimens. Importantly, capmatinib single agent activity was minimal or absent in all tested models, consistent with the fact that none of these models harbored any MET-activating alteration. The capmatinib + anti-PD-1 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 upon addition of capmatinib to immune therapies were also seen in a second, independently performed series of studies with syngeneic mouse models (Glodde et al 2017). As a mechanistic explanation, a reactive production of HGF in the inflamed tumor microenvironment, leading to recruitment of immunosuppressive MET-positive neutrophils, has been proposed. Prevention of this negative feedback loop by capmatinib might explain the benefit of the combination treatment. Further, the additional mechanisms involving MET-positive immune cells discussed above (Section 1.1) may also contribute to the observed enhancement of anti-tumor immunity when adding capmatinib to IO treatments.

1.1.3.2 Clinical experience

The combination of capmatinib with a PD-1 inhibitor, either nivolumab or spartalizumab, is currently being evaluated in clinical trials. Overall, no significant drug-drug interactions (DDI) have been observed in these studies from pharmacokinetic assessment in the relative populations. For safety and efficacy data, refer to Section 1.1.3.2.1 and Section 1.1.3.2.2.

1.1.3.2.1 Combination of Capmatinib and Nivolumab in NSCLC

The combination of capmatinib and the PD-1 inhibitor nivolumab is currently being explored in study CEGF816X2201C. This ongoing study is a phase II, open-label trial of capmatinib in combination with nivolumab in adult subjects with advanced IO therapy-naive NSCLC with "MET-high" status (defined as cMET IHC 3+, or IHC 2+ & Gene Copy Number (GCN) ≥ 5, or MET exon 14 mutations) or "MET-low" status (defined as not meeting the criteria for MET-high). As of 10-Sep-2019, 46 patients have been enrolled and treated with capmatinib 400 mg BID + nivolumab 3 mg/kg q2 weeks.

Overall, the safety profile of the combination was manageable. Forty-six patients (100%) experienced AEs of any grade, regardless of causality. The most common AEs of any grade were nausea (54.3%), vomiting (39.1%), blood creatinine increased (32.6%), edema peripheral (32.6%), increased amylase (32.6%), asthenia (32.6%), lipase increased (28.3%), decreased appetite (26.1%), diarrhea (23.9%), pyrexia (23.9%), hypoalbuminaemia (23.9%) and anaemia (21.7%); the majority of AEs were Grade 1/2.

Forty-three patients (93.5%) experienced AEs of any grade suspected to be related to study treatment. The most frequent AEs of any grade suspected to be related to study treatment were nausea (52.2%), edema peripheral (32.6%); increased blood creatinine (30.4%), vomiting (26.1%), increased amylase (26.1%), decreased appetite (23.9%), diarrhoea (23.9%), asthenia (23.9%) and lipase increased (23.9%); the majority of AEs were Grade 1/2.

For further details, please refer to the capmatinib Investigator's Brochure.

These preliminary data support the tolerable combination of capmatinib with a PD-1 inhibitor in NSCLC.

1.1.3.2.2 Combination of Capmatinib and Spartalizumab

Capmatinib in combination with spartalizumab is currently being evaluated in three studies: 1) a dose escalation and expansion study CINC280X2108 in subjects with hepatocellular carcinoma (HCC), 2) a randomized phase II study in subjects with advanced NSCLC that have progressed following treatment with one platinum-doublet and one PD-1 inhibitor (CINC280D2201), and 3) a phase II platform study in subjects with advanced melanoma (CPDR001J2201). While enrollment is completed in study CINC280X2108, it is still ongoing in the other two studies; therefore no data are currently available from studies CINC280D2201 and CPDR001J2201. For additional information, please refer to the current capmatinib Investigator's Brochure.

CINC280X2108 is an ongoing phase Ib/II, open-label, multi-center study of capmatinib in combination with spartalizumab versus spartalizumab alone, in advanced IO treatment-naive HCC after sorafenib failure.

As of 01-Sep-2019, a total of 89 patients have been enrolled in the study. Twenty-seven patients were treated in the dose escalation part (phase Ib) at three dose levels: 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 spartalizumab. The RP2D was determined to be capmatinib 400 mg BID in combination with spartalizumab 300 mg Q3W. Thirty patients were enrolled into the spartalizumab single agent arm of the phase II part of the study and 32 patients were enrolled into the combination arm of capmatinib and spartalizumab.

Only data from patients treated with capmatinib in combination with spartalizumab are described below (Phase Ib and Phase II, N=59 patients). Fifty-five patients (93.2%), experienced AEs of any grade. The most common AEs, regardless of causality were: edema peripheral (47.5%), nausea (40.7%), decreased appetite (32.2%), pyrexia (32.2%), diarrhoea (28.8%), asthenia (27.1%), alanine aminotransferase increased (23.7%), aspartate aminotransferase increased (23.7%), blood bilirubin increased (23.7%), hypoalbuminemia (23.7%) and vomiting (23.7%). The majority of AEs were grade 1/2.

Forty-nine patients (83%) experienced AEs of any grade, suspected to be related to study treatment. The most frequent AEs suspected to be related to study treatment were nausea (30.5%), edema peripheral (28.8%), vomiting (23.7%) and decreased appetite (20.3%). The majority of AEs were Grade 1/2.

Forty-one patients (69.5%) experienced Grade 3/4 AEs regardless of causality. Twenty-nine patients (49.1%) had Grade 3/4 AEs suspected to be related to study treatment, the most frequent AEs suspected include asthenia (10.2%), aspartate aminotransferase increased (6.8%) and lipase increased (6.8%).

At least one SAE regardless of causality has been reported for 19 patients (32.2%). Nine patients (15.2%) experienced the following SAEs suspected of being related to study treatment. For further details please refer to the capmatinib Investigator's Brochure.

The safety data support combining capmatinib with spartalizumab in NSCLC patients in the current protocol. However, as no data exist for the combination in treatment-naive METΔex14 NSCLC, this study has been designed with a single arm open label run-in part preceding the randomized part.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of capmatinib in combination with spartalizumab in treatment naive patients with EGFR wt, ALK rearrangement negative advanced NSCLC, harboring METΔex14 mutations.

METΔex14 mutated NSCLC is rare, occurring in 2-4% of the total NSCLC population. METΔex14 mutations are associated with poor prognosis and poor response to standard therapies, including immunotherapy. Based on this, and on the promising data with single agent capmatinib demonstrated in the treatment of naive subjects, capmatinib can be considered the appropriate therapy for this population.

An ongoing phase II study in the METΔex14 mutated NSCLC population CINC280A2201 showed single agent efficacy for capmatinib monotherapy in both treatment-naive and previously treated subjects. ORR by BIRC was 67.9% (95% CI: 47.6, 84.1) in the treatment-

naive setting, with a median DOR of 11.14 months (95% CI: 5.55, NE) and a median PFS by BIRC of 9.69 months (Anon 2019, Wolf et al 2019).

If tolerable, combination of targeted and IO therapies in a molecularly selected indication has the potential to result in clinical efficacy that is superior to the targeted therapy alone (Long et al 2019, see also Section 1.1). MET inhibitors may be a particularly attractive type of targeted therapy for combination with IO agents, since the MET signaling pathway is suggested to have a role in immune modulation, and preclinical data indicate that capmatinib has synergistic effects with checkpoint inhibitors (Section 1.1.3.1).

By combining capmatinib with spartalizumab in METΔex14 mutated NSCLC, we expect improved efficacy compared to direct targeting of the oncogenic driver by capmatinib monotherapy, because spartalizumab can promote an additional anti-tumor immune response that may be further enhanced by the immunomodulatory effect of capmatinib. This study will be the first to evaluate the activity of capmatinib in combination with a PD-1 inhibitor in METΔex14 mutated NSCLC in the treatment-naive setting.

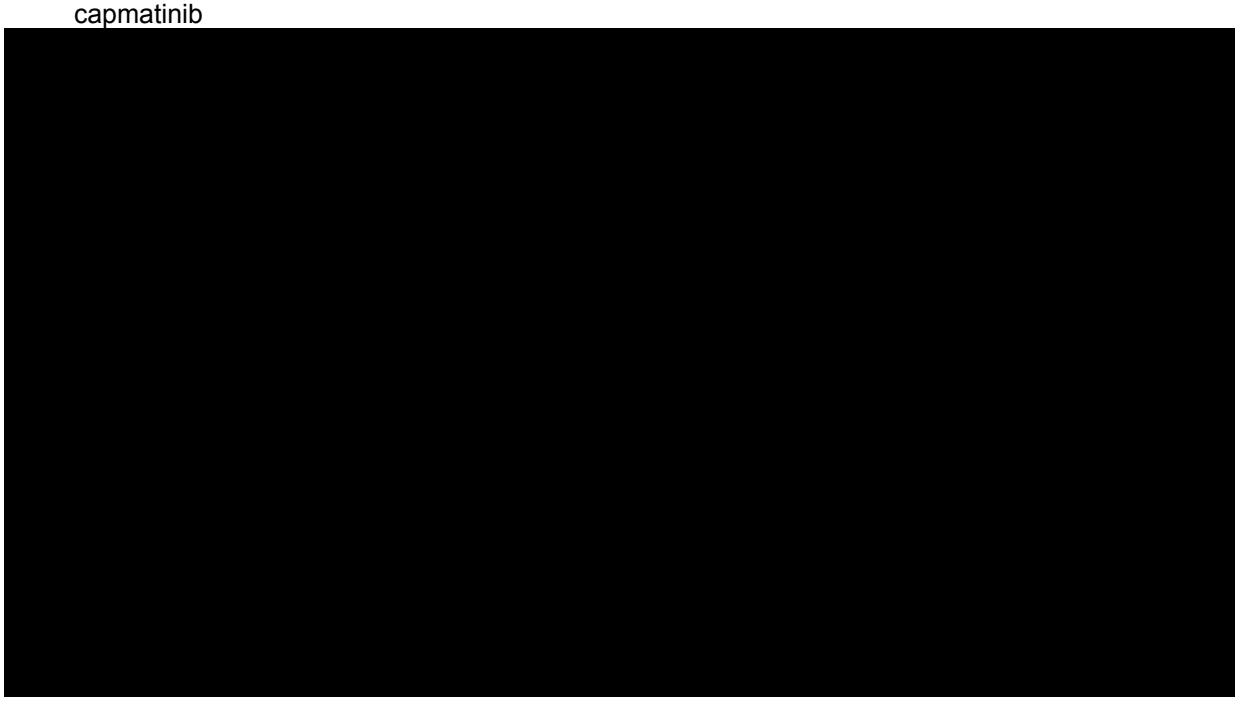
2 Objectives, related endpoints and estimands

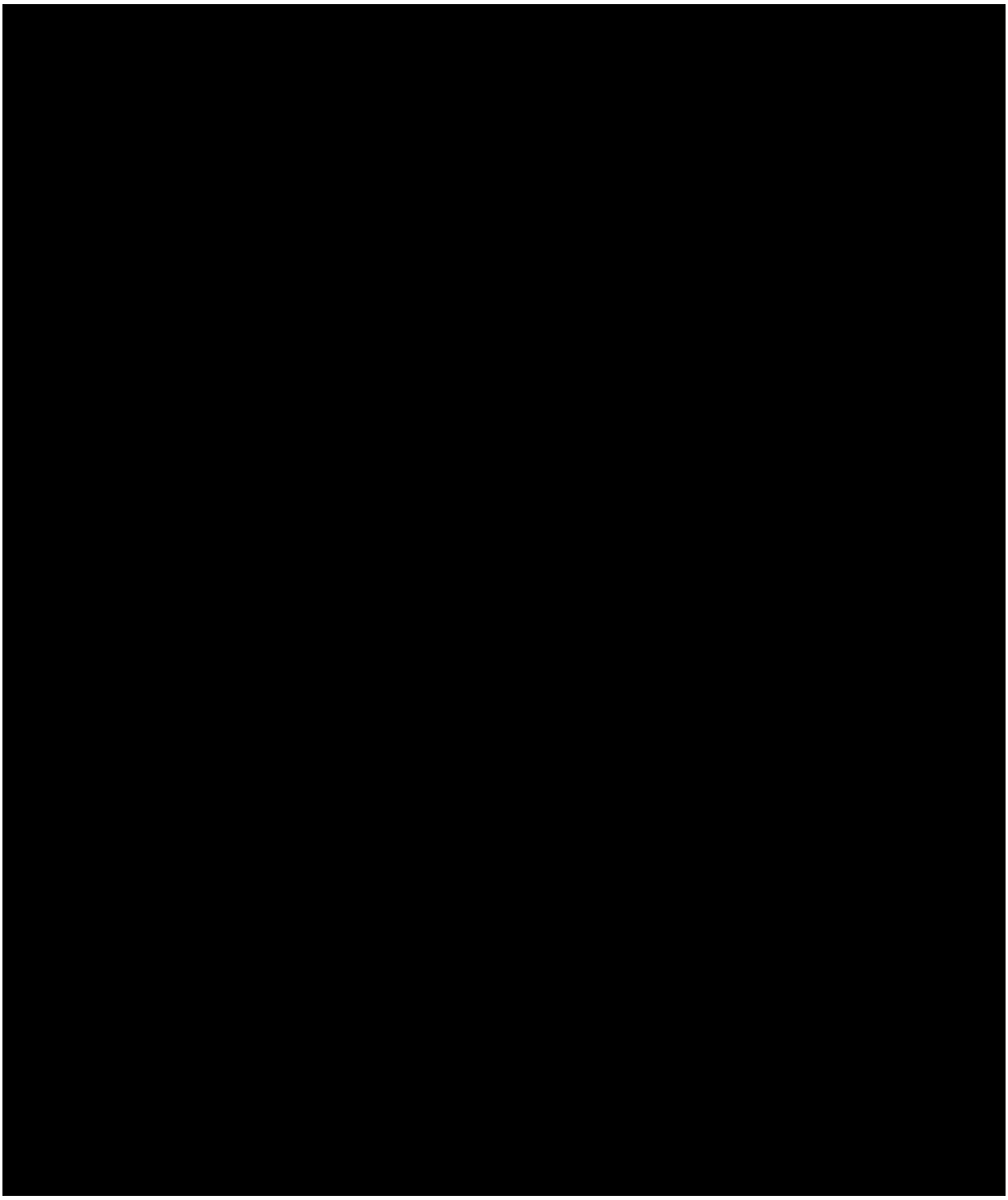
Objectives and related endpoints are described in Table 2-1 below.

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary Objectives	**Endpoints for primary objectives**
Run-in part To evaluate the anti-tumor activity of capmatinib in combination with spartalizumab	Overall Response Rate (ORR) by investigator assessment as per RECIST 1.1
Randomized part To compare the efficacy of capmatinib in combination with spartalizumab versus capmatinib plus placebo	Progression Free survival (PFS) by BIRC as per RECIST 1.1
Key Secondary Objective	**Endpoint for key secondary objective**
Randomized part To compare overall survival of capmatinib in combination with spartalizumab versus capmatinib plus placebo	Overall survival (OS)
Other Secondary Objectives	**Endpoints for other secondary objectives**
Run-in part • To assess safety and tolerability of capmatinib in combination with spartalizumab	• Safety: incidence and severity of AEs and SAEs, changes in laboratory values, vital signs and ECGs. Any clinically significant lab, vital signs, ECG abnormalities will be captured as an AE • Tolerability: dose interruptions, reductions, and dose intensity
• To further evaluate the anti-tumor activity of capmatinib in combination with spartalizumab	• Disease Control Rate (DCR) and PFS by investigator assessment as per RECIST 1.1

Objectives	Endpoints
• To evaluate the PK of capmatinib and spartalizumab	• Concentrations and derived PK parameters of capmatinib and spartalizumab
Randomized part	
• To assess safety and tolerability of capmatinib in combination with spartalizumab versus capmatinib plus placebo	• Safety: incidence and severity of AEs and SAEs, changes in laboratory values, vital signs and ECGs. Any clinically significant lab, vital signs, ECG abnormalities will be captured as an AE • Tolerability: dose interruptions, reductions, and dose intensity
• To further evaluate the anti-tumor activity of capmatinib in combination with spartalizumab versus capmatinib plus placebo	• PFS by investigator assessment as per RECIST 1.1 • DCR, DOR, ORR and TTR by BIRC and investigator assessment as per RECIST 1.1
• To evaluate patient reported outcomes of capmatinib in combination with spartalizumab versus capmatinib plus placebo	• Change from baseline in EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L • Time to definitive 10 points deterioration symptom scores for pain in chest, coughing and dyspnea per QLQ-LC13 questionnaire as three primary PRO variables of interest and time to definitive deterioration in global health status/QoL, shortness of breath and pain per EORTC QLQ-C30 as secondary PRO variables of interest.
• To evaluate the PK of capmatinib and spartalizumab	• PK concentrations
• To evaluate the prevalence and incidence of immunogenicity of spartalizumab in combination with capmatinib	• Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on treatment with spartalizumab





2.1 Primary estimand

Part 1: Single Arm Run-In Part

The primary scientific interest is to estimate the effect of capmatinib in combination with spartalizumab in terms of overall radiological response by investigator assessment as per RECIST 1.1 in first line NSCLC with METΔex14 mutation.

The primary estimand is characterized by the following attributes:

1. Population: adult patients with NSCLC with METΔex14 mutation in first line setting. Further details on the population are provided in Section 5.
2. Treatment: capmatinib in combination with spartalizumab without any new anti-neoplatic therapy. Further detail about the treatment is provided in Section 6.
3. Variable: Best Overall Response (BOR) defined as the best response recorded from the start of the treatment until disease progression/recurrence by investigator assessment as per RECIST 1.1
4. Intercurrent events:
   - Discontinuation of spartalizumab for any reason (treatment policy strategy)
   - Discontinuation of tumor assessment follow up with approval of protocol amendment 01 (while on treatment strategy)
   - Any public health emergency as declared by local or regional authorities, e.g., pandemic, epidemic or naturadisaster (treatment policy strategy)
   - New anti-neoplastic therapy (while on treatment strategy)

Details on how to handle the intercurrent events are provided in Section 12.4.1.3.

5. Summary measure: Proportion of subjects with a confirmed CR/PR as BOR, with its corresponding two-sided exact binomial 95% CI.

Part 2: Randomized Part

Following the study enrollment halt, Part 2 will not be initiated.

The primary scientific question of interest is: What is the relative effect of the two treatment strategies in prolonging time to radiological progression by BIRC per RECIST 1.1 or death in first line NSCLC with MET exon 14 skipping mutation, regardless of study treatment discontinuation or start of new anti-neoplastic therapy?

The primary estimand is characterized by the following attributes:

1. Population: adult patients with NSCLC with MET exon 14 skipping mutation in first line setting. Further details on the population are provided in Section 5.
2. Treatment: Capmatinib in combination with spartalizumab versus capmatinib in combination with placebo. Further detail about the treatment is provided in Section 6.
3. Variable: PFS by BIRC as per RECIST 1.1
4. Intercurrent events:
   - Discontinuation of study treatment for any reason before radiological progression or death due to any cause
   - New anti-cancer therapy before radiological progression or death due to any cause

- Radiological progression or death observed after two or more missing tumor assessments
- Lack of post-baseline tumor assessment

Details on how to handle the intercurrent events are provided in Section 12.4.1.3.

5. Summary measure: PFS hazard ratio (capmatinib plus spartalizumab versus capmatinib plus placebo) along with 95% confidence interval, estimated using a Cox proportional hazard model stratified by the randomization stratification factors.

2.2 Secondary estimand

Part 1: Single Arm Run-In Part

Following the approval of protocol amendment 01, this section will no longer be applicable.

The secondary scientific question of interest is: What is the effect of capmatinib in combination with spartalizumab in improving the duration of the radiological response by BIRC as per RECIST 1.1 in first line NSCLC with MET exon 14 skipping mutation, regardless of study treatment discontinuation or start of new anti-neoplastic therapy?

The secondary estimand is characterized by the following attributes:

1. Population: adult patients with NSCLC with MET exon 14 skipping mutation in first line setting who have had a confirmed response of either CR or PR as assessed by BIRC. Further details on the population are provided in Section 5.
2. Treatment: Capmatinib in combination with spartalizumab. Further detail about the treatment is provided in Section 6.
3. Variable: Duration of Response (DOR) by BIRC as per RECIST 1.1
4. Intercurrent events:
   - Discontinuation of study treatment for any reason before radiological progression or death due to any cause
   - New anti-cancer therapy before radiological progression or death due to any cause
   - Radiological progression or death observed after two or more missing tumor assessments

Details on how to handle the intercurrent events are provided in Section 12.5.2.

5. Summary measure: Median DOR with it corresponding 95% CI estimated using Kaplan-Meier method.

Part 2: Randomized Part

Following the study enrollment halt, Part 2 will not be initiated.

The secondary scientific question of interest is: What is the relative effect of the two treatment strategies in prolonging time to death in first line NSCLC with MET exon 14 skipping mutation, regardless of study treatment discontinuation or start of new anti-neoplastic therapy?

The key secondary estimand is characterized by the following attributes:

1. Population: adult patients with NSCLC with MET exon 14 skipping mutation in 1L setting. Further details on the population are provided in Section 5.
2. Treatment: Capmatinib in combination with spartalizumab regardless of being followed by any standard of care (SOC) versus capmatinib in combination with placebo regardless of being followed by any SOC. Further detail about the treatment is provided in Section 6.
3. Variable: OS
4. Intercurrent events:
   - Discontinuation from study for any reason
   - New anti-cancer therapy

Details on how to handle the intercurrent events are provided in Section 12.5.1.1

5. Summary measure: OS hazard ratio (capmatinib plus spartalizumab versus capmatinib plus placebo) along with 95% confidence interval, estimated using a Cox proportional hazard model stratified by the randomization stratification factors.

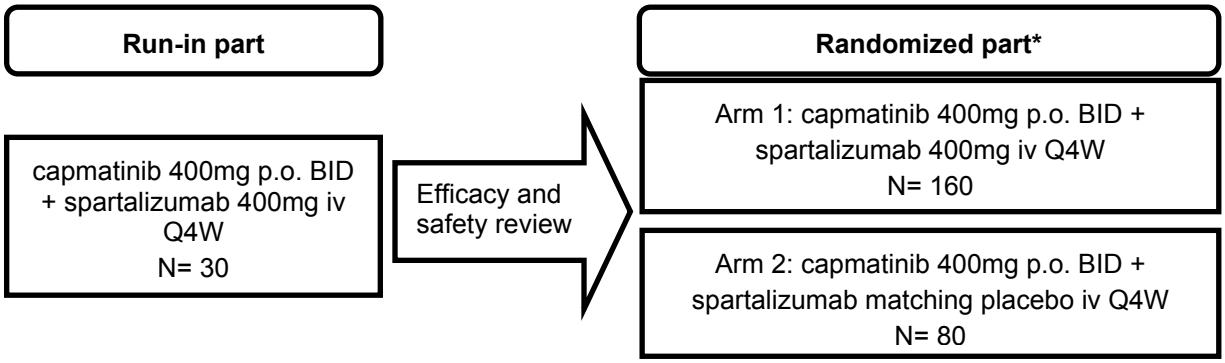
3 Study design

This is a two-part, multicenter, phase II study to evaluate the efficacy and safety of capmatinib in combination with spartalizumab in treatment of naive patients with EGFR wt, ALK rearrangement negative advanced NSCLC, harboring METΔex14 mutations.

The study consists of a single arm open label run-in part followed by a double-blind, placebo controlled, randomized part.

The study will enroll approximately 270 subjects. An overview of the study design is provided in Figure 3-1.

Figure 3-1 Study design



*Following the study enrollment halt in Part 1, spartalizumab treatment has been discontinued and the randomized part will not be initiated.

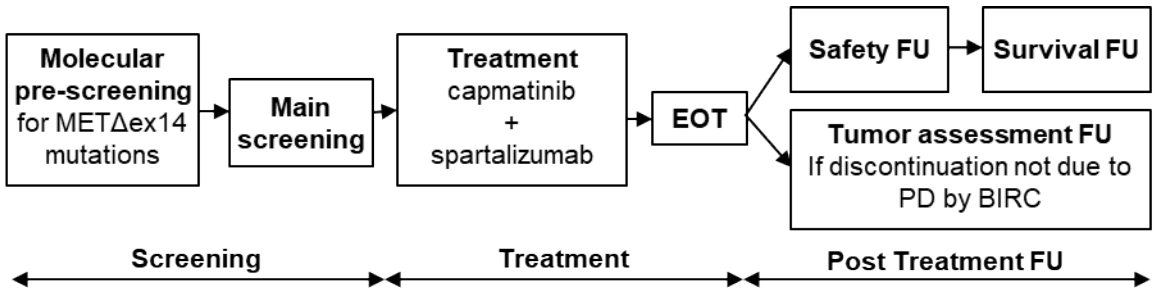
Part 1: Single Arm Run-in Part

Approximately 30 subjects will be treated with the capmatinib and spartalizumab combination during the run-in part of the study (Part 1). The primary objective of Part 1 is to assess the ORR by investigator assessment as per RECIST 1.1 of the combination of capmatinib with spartalizumab.

Refer to Figure 3-2 for an overview on the study design of Part 1.

Figure 3-2 Study design Part 1

Following the approval of protocol amendment 01, tumor assessment FU and survival FU will not be performed



EOT: end of treatment; FU: follow-up

Part 2: Randomized Part

Following the study enrollment halt, Part 2 will not be initiated.

In the randomized part (Part 2), approximately 240 subjects will be randomized in a 2:1 ratio to the following treatment arms:

- Arm 1: capmatinib plus spartalizumab (n=160)
- Arm 2: capmatinib plus spartalizumab matching placebo (n=80).

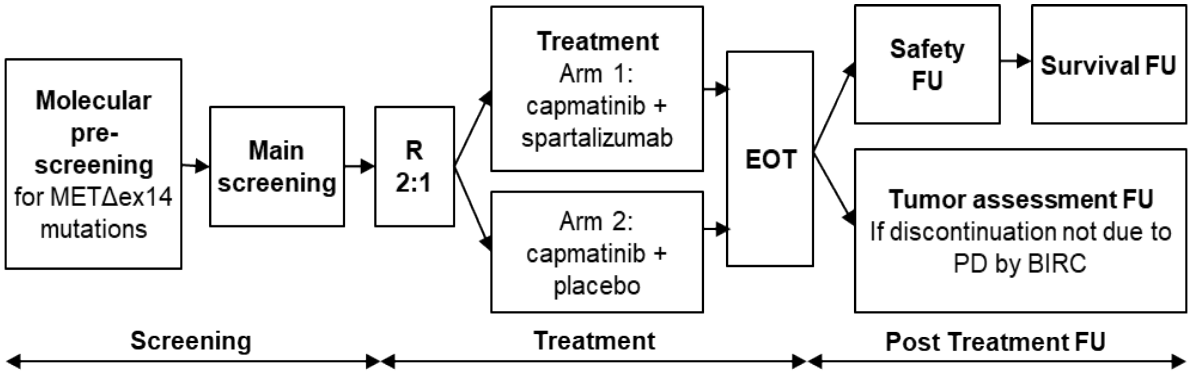
The randomization will be stratified by presence or absence of brain metastasis at baseline (as assessed by investigator per RECIST 1.1) and PD-L1 expression (<1%, or 1-49%, or ≥50%), assessed either locally using Dako PD-L1 IHC 22C3 pharmDx, or at a Novartis-designated central lab.

The primary objective of Part 2 is to assess the PFS of the combination of capmatinib plus spartalizumab compared to capmatinib plus placebo as determined by BIRC. OS will be assessed as the key secondary objective. One interim analysis for PFS and a maximum of three interim analyses for OS are planned; the purpose and the timing of these analyses are described in Section 4.4.

After the primary analysis of PFS, if the primary endpoint is met, investigators and subjects will continue to remain blinded to study treatment and all subjects will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at any of the interim analyses).

Refer to Figure 3-3 for an overview on the study design of Part 2.

Figure 3-3 Study design Part 2



R: randomization; EOT: end of treatment; FU: follow-up.

Overview of study visit flow (Part 1 and Part 2)

For all subjects tumor molecular pre-requisites will be assessed during screening. EGFR and ALK status will be verified based on tests performed locally as part of standard clinical practice, while MET mutation status will be assessed at a Novartis-designated central laboratory during molecular pre-screening, unless previously determined locally (only local assays agreed by Novartis will be accepted). Additional information regarding the molecular pre-screening and the main screening are provided respectively in Section 8.1.1 and Section 8.1.2.

Subjects with NSCLC of pure squamous cell histology do not need to be tested for an EGFR mutation or ALK rearrangement, however, subjects with pure squamous cell histology already known to have EGFR mutations in exons 19 and 21 or ALK-positive rearrangement will be excluded. Once all eligibility criteria are confirmed, subjects will receive capmatinib 400 mg BID in combination with spartalizumab 400 mg or placebo Q4W in a 28-day cycle.

Subjects will be treated until they experience unacceptable toxicity, disease progression per RECIST 1.1 as determined by investigator assessment (with or without confirmation by BIRC), and/or treatment is discontinued at the discretion of the investigator or the subject. A complete list of the circumstances requiring study treatment discontinuation is provided in Section 9.

Study treatment may be continued beyond disease progression per RECIST 1.1 if, in the judgment of the investigator, there is evidence of clinical benefit, and the subject wishes to continue on the study treatment (for additional details please refer to Section 6.1.4).

After study treatment discontinuation, an end of treatment visit will be performed, all subjects will then enter the safety follow-up period, which will last for 150 days after last dose of spartalizumab or 30 days after last dose of capmatinib, whichever is longer. For subjects who are transferred to another clinical study or alternative treatment option to continue capmatinib treatment at end of study, no further collection of safety data will be required as part of this study (for details please refer to Section 9.2.1).

4 Rationale

4.1 Rationale for study design

This study has been designed as a phase II, multicenter study consisting of two parts.

- Part 1: Single arm run-in part of capmatinib in combination with spartalizumab
- Part 2: Randomized part of capmatinib in combination with spartalizumab versus capmatinib plus placebo

Following the study enrollment halt during Part 1, Part 2 will not be initiated.

Part 1: Single Arm Run-in Part

Part 1 of the study was designed to assess the efficacy and safety of capmatinib in combination with spartalizumab in treatment-naive adult subjects with advanced NSCLC harboring METΔex14 mutation. Based on the safety observed during Part 1, the decision was made not to open Part 2.

Thirty-one patients were treated in Part 1 of the study.

The primary objective of Part 1 of the study is to evaluate the anti-tumor activity of capmatinib in combination with spartalizumab. The primary outcome measure of anti-tumor activity is ORR according to RECIST 1.1 and as determined by investigator assessment. ORR is an endpoint that can be used to assess earlier the efficacy of a treatment in studies with small sample size (FDA-industry guidance 2018). Given the efficacy observed with capmatinib single agent in the same patient population (Anon 2019, Wolf et al 2019), ORR can be used as a surrogate endpoint to predict the clinical benefit of capmatinib in combination with spartalizumab in the context of the single arm run-in part of the study (FDA-industry guidance 2015).

Part 2: Randomized Part

Upon review of safety data and confirmation of anti-tumor activity in Part 1, Part 2 will be initiated (see Section 12.8). Part 2 of the study will compare the efficacy and safety of capmatinib in combination with spartalizumab versus capmatinib plus placebo in treatment-naive adult subjects with advanced NSCLC harboring METΔex14 mutation.

Approximately 240 subjects will be randomized in a 2:1 ratio to either capmatinib in combination with spartalizumab or capmatinib plus placebo.

Patients will be stratified for tumor PD-L1 expression, a predictor of response to PD-1/PD-L1 inhibitors, and presence or absence of brain metastases, a strong prognostic factor in NSCLC, to identify differential efficacy in the respective stratification groups.

The primary objective of Part 2 of the study is to demonstrate that capmatinib in combination with spartalizumab is superior to capmatinib plus placebo in terms of efficacy. The primary endpoint is PFS (based on BIRC as per RECIST 1.1), and the key secondary endpoint is OS.

4.2 Rationale for dose/regimen and duration of treatment

The feasibility of the combination of capmatinib with a checkpoint inhibitor has been confirmed in two studies CINC280X2108 and CEGF816X2201C. For details, please refer to Section 1.1.3.2.

The combination of capmatinib with spartalizumab has been evaluated in study CINC280X2108 conducted in hepatocellular carcinoma (HCC) where the RP2D was declared at 400 mg BID for capmatinib in combination with 300 mg spartalizumab Q3W.

In study CPDR001X2101 pharmacokinetic and safety data across tested dose levels supported the declaration of two RP2Ds for spartalizumab as single agent: 300 mg Q3W and 400 mg Q4W. Based on the population PK model simulations, both regimens are expected to be safe and efficacious (for additional information refer to Section 1.1.2.2), therefore two RP2Ds were declared to allow more convenient scheduling of treatments for subjects receiving combination therapy with spartalizumab.

In this study, the 400 mg Q4W schedule was selected for spartalizumab based on scheduling convenience for patients in the setting of advanced NSCLC.

4.3 Rationale for choice of combination and comparator drugs

4.3.1 Rationale for choice of combination

Capmatinib was granted accelerated approval by the FDA in the treatment-naive and in pretreated NSCLC with METΔex14 mutations regardless of line of treatment based on safety and efficacy data from study CINC280A2201 (Wolf et al 2019). Other trials have demonstrated that the combination of capmatinib with spartalizumab is feasible from a safety perspective (Section 1.1.3.2.2). Emerging clinical data from a melanoma trial, where direct targeting of the oncogenic drive (BRAF) is combined with the immune stimulator spartalizumab, suggests that deep and durable responses can be achieved with the concept of combining targeted and IO therapy (Long et al 2019).

In addition, inhibition of MET by pharmacological or genetic means can enhance T cell mediated anti-tumor immunity in a variety of treatment regimens and mouse tumor models (including melanoma lung, breast, and colon cancer models). (Glodde et al 2017) proposed a model in which capmatinib counteracts an HGF-driven negative feedback loop in a T cell inflamed tumor microenvironment, activated immune cells and/or tumor-associated stroma secrete HGF, which is mirrored by an increased serum HGF level. As a consequence, MET-positive neutrophils are mobilized and invade tumor and adjacent lymph nodes, where they acquire immunosuppressive properties, dampening the T cell response (Glodde et al 2017).

In order to independently reproduce these results, the combination of anti-PD-1 and capmatinib was tested in two syngeneic mouse models at Novartis RD-2017-00370. Combination treatment led to increased T cell infiltration in the short term, and an improved anti-tumor immune response with a higher cure rate than either single agent in the long term. The *in vivo* studies were extended in a second model (cervical carcinoma) that was generated at Novartis in a genetically engineered mouse strain with error-prone DNA (deoxyribonucleic acid) replication, which also leads to a high mutation burden. Again, addition of capmatinib to anti-PD-1 therapy led to an increased cure rate, while the MET inhibitor was largely inactive on its own.

Besides these direct functional data in mouse models, the reported immunosuppressive effects of HGF/MET on dendritic cells and T cells (Section 1.1) further support the rationale for combining anti-PD-1 and capmatinib, because both agents have the potential to enhance T cell mediated anti-tumor immunity through complementary mechanisms. While inhibition of HGF/MET signaling is expected to enhance antigen presentation and T cell stimulation by dendritic cells and potentially even increase cytotoxicity of a subset of T cells, anti-PD-1 antibodies will prevent suppression of T cell function through PD-L1 expressed on tumor cells or other immune cells.

Combined treatment with capmatinib and spartalizumab of METΔex14 mutated NSCLC is expected to result in improved efficacy compared to each single agent due to direct targeting of an oncogenic driver (MET) as well as more efficient stimulation of an anti-tumor immune response than with PD-1 blockade alone.

4.3.2 Rationale for choice of comparator drugs

Capmatinib montherapy has shown promising anti-tumor activity in treatment-naive and in pretreated NSCLC with METΔex14 mutations in study CINC280A2201. In the first line setting ORR was 67.9% (see Section 1.1.1.2), supporting capmatinib single agent as an appropriate comparator in first line in this particular subset of NSCLC patients.

Currently available therapies, IO and chemotherapy platinum-doublets, are less effective in the METΔex14 population compared to unselected NSCLC and the role of PD-L1 expression as predictor of response to IO is less clear (Sabari et al 2017). Triplet/quadruplet combinations of chemotherapy and IO are less likely to be tolerated by patients with METΔex14 mutated NSCLC who are commonly older and more frail than the general NSCLC population (Schrock et al 2016).

In summary, although not yet evaluated in a randomized trial versus IO or chemotherapy due to the challenges of conducting such a trial in a very small patient population, the clinical efficacy and safety of capmatinib monotherapy in first line METΔex14 mutated NSCLC suggests that it is an appropriate comparator for the capmatinib + spartalizumab combination.

4.4 Purpose and timing of interim analyses

Part 1: Single Arm Run-in Part

No formal interim analysis is planned for Part 1 of the study. Based on the safety observed during Part 1, the decision was made not to open Part 2.

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated.

One efficacy interim analysis for PFS is planned when approximately 145 PFS events (75% information fraction) have been observed and all subjects have been randomized to the study. The primary intent of the efficacy interim analysis is to report early outstanding efficacy results in terms of PFS if the pre-specified threshold for significance is crossed.

At the time of the interim PFS analysis, the first interim analysis for OS will be conducted, and at this time approximately 97 deaths (49% information fraction) are expected to be observed. A second interim analysis for OS is planned to be conducted at the time of the primary PFS analysis when 193 PFS events have been observed, and at this time approximately 146 deaths (74% information fraction) are expected to be observed. A third interim analysis for OS is planned to be conducted approximately 15 months after the primary PFS analysis, and at this time approximately 167 deaths (85% information fraction) are expected to be observed. A hierarchical testing procedure will be used in this study where OS is tested only if the respective PFS analysis is statistically significant.

Additional details on the interim analyses for PFS and OS are provided in Section 12.7.

4.5 Risks and benefits

All subjects treated in this study will receive capmatinib, which has an established efficacy and safety profile in the study population.

In addition, subjects enrolled in this study will have unresectable stage IIIB, IIIC or IV NSCLC and no other potentially curative treatment. Given the clinical and molecular characteristics of METΔex14 mutated NSCLC, even patients in the treatment naive setting have few therapeutic options and the established standard of care has limited benefit in this patient population.

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

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as by close clinical monitoring and oversight. As with any clinical study, there may be unforeseen risks with the study treatment, which could be serious. The specific risks for each compound are discussed below. For further details, refer to the toxicity data provided in the capmatinib Investigator's Brochure and in the spartalizumab Investigator's Brochure.

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that, in order to participate in the study, they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any lack of clarity about a subject's willingness or capability to comply with these requirements, they should not enter or continue in the study.

4.5.1 Capmatinib

Based upon the clinical experience with capmatinib to date, the overall risk-benefit assessment of capmatinib is considered favorable. The data from study CINC280A2201 show that capmatinib is generally well tolerated and has a manageable safety profile. The safety profile in the METΔex14 mutated NSCLC population is consistent with the safety profile of capmatinib across multiple clinical studies. In the context of the significant clinical benefit

observed for this patient population with limited effective therapeutic options, the overall safety profile is acceptable, and the benefit/risk favorable (see Section 1.1.1.2).

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

In addition, pancreatic events (e.g. amylase and lipase increase), and liver function test alterations (ALT and/or AST and/or bilirubin increase) have been observed in patients treated with capmatinib. To date, a direct toxic effect of capmatinib on pancreas cannot be definitively identified. Caution is recommended when capmatinib is administered in combination with other anticancer drugs with a known risk of hepatotoxicity.

Pneumonitis and Interstitial Lung Disease (ILD) have been reported from both capmatinib single agent and combination studies with EGFR TKIs, including events with fatal outcomes. Investigators are advised to carefully monitor subjects for signs and symptoms of pneumonitis and implement dose modification and follow-up evaluations described in the protocol in all capmatinib studies, both single agent and in combination studies.

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

For further information on potential toxicities, please refer to the current capmatinib Investigator's Brochure.

4.5.2 Spartalizumab

Spartalizumab is a humanized mAb which belongs to a class of agents known as immune-checkpoint inhibitors, specifically anti-PD-1. This class of compounds has demonstrated significant improvement in efficacy combined with a tolerable and manageable safety profile, supporting regulatory approvals in various indications.

Immune-checkpoint inhibitors of this class may be associated with the occurrence of immune-related adverse events (irAEs). In general, irAEs can potentially involve every organ system but gastrointestinal (GI) (e.g. diarrhea, colitis), dermatologic (e.g. rash, pruritus), hepatic (e.g. hepatitis), pulmonary (e.g. pneumonitis), renal (e.g. nephritis) and endocrine toxicities (e.g. hypothyroidism, hyperthyroidism, type I diabetes, hypophysitis including hypopituitarism and adrenal insufficiency) are typically the most frequent. Other irAEs may rarely include the nervous system (e.g. encephalitis, Guillain-Barre syndrome, myasthenia gravis), eye (e.g. uveitis, vision changes), musculo-skeletal system (e.g. myositis, arthritis), pancreas (e.g. pancreatitis), cardio-vascular system (e.g. vasculitis, myocarditis) or blood system (e.g. anemia, cytopenias), and severe skin reactions such as toxic epidermonecrolysis or Stevens-Johnson syndrome. Furthermore, complications in patients with bone marrow or solid organ transplant have been reported (e.g. organ rejection, severe graft-versus-host disease).

These side effects are generally manageable and reversible with dose interruption and administration of corticosteroids and/or other immunosuppressants. However, fatal events have been reported in some cases with checkpoint inhibitors; furthermore, some events like endocrinopathies may require life-long hormonal replacement. While most irAEs are expected

to occur during the treatment with spartalizumab, onset may be delayed and irAEs may also occur after discontinuation of study treatment (Spain et al 2016, Hofmann et al 2016, Champiat et al 2016, Haanen et al 2017, Brahmer et al 2018). In addition, mAbs can be associated with infusion-related reactions some of which can be severe; these are often immediate and usually occur within minutes of the exposure to the study drug. Therefore, infusions should take place in a facility with appropriate resuscitation equipment available at the bedside and a physician readily available, and patients monitored for respective signs and symptoms. Patients who experience severe or life-threatening irAEs or infusion reactions may need to permanently discontinue spartalizumab (see Section 6.5 for further guidance).

Clinical experience with spartalizumab to date suggests that it can cause irAEs. It is therefore important to be vigilant and carefully identify events that may be suggestive of potential irAEs, as their appearance may be sub-clinical (for example an asymptomatic laboratory abnormality), and early diagnosis is critical for appropriate management and possibly prevent complications. Serological, immunological and histological assessments (such as biopsy of the affected tissue) should be performed as deemed appropriate by the investigator to verify the potential immune-mediated nature of the AE and to exclude alternative diagnoses or disease progression. Following appropriate and complete evaluation, an empiric trial of corticosteroids may contribute to the identification of irAEs.

Refer also to the latest version of the spartalizumab Investigator's Brochure for additional details on clinical and preclinical safety.

4.5.3 Capmatinib combined with spartalizumab

Both capmatinib and spartalizumab are well tolerated as single agents. There is no pharmacological or clinical evidence that would anticipate any cumulative, interactive or unexpected toxicity of the compounds if given in combination and pharmacokinetic DDI is anticipated to be low.

Data from the dose escalation and expansion study CINC280X2108 in subjects with HCC confirms that the safety profile of the combination of capmatinib and spartalizumab in this disease setting is manageable.

The most frequent safety findings suspected to be related to treatment with the combination include peripheral edema, diarrhea, nausea and vomiting, pyrexia, fatigue, asthenia, AST and ALT elevations, and pruritus.

In Study CPDR001J2201, one subject with metastatic melanoma experienced myocarditis and hepatitis approximately two months after initiation of combination therapy with capmatinib and spartalizumab. The subject was treated with prednisolone. At the time of reporting, hepatitis was fully recovered and myocarditis was ongoing.

For further detail on potential adverse events with the combination of capmatinib and spartalizumab please refer to Section 1.1.3.2 of this protocol.

A decision to halt study enrollment and to discontinue spartalizumab treatment in all ongoing subjects was taken based on the lack of tolerability observed with the combination of capmatinib and spartalizumab in Part 1 of this trial. All ongoing subjects may continue to be treated with single agent capmatinib. Given that capmatinib has a well established safety profile as

monotherapy and a proven benefit in first line NSCLC population with MET exon 14 skipping mutation, the risk-benefit balance of the trial subjects is considered favorable.

4.6 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities, e.g, pandemic, epidemic or natural disaster, mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol.

Prior to implementation of mitigation procedures, Novartis should be notified of the public health emergency, and the mitigation procedues must be permitted/approved by local or regional Health Authorities and Ethics Committees as appropriate.

5 Population

This study will enroll adult male and female patients with stage IIIB, IIIC or IV NSCLC harboring METΔex14 mutations, who have not received prior systemic therapy for advanced/metastatic disease.

Patients enrolled in the study are not permitted to participate in any additional, parallel, investigational drug or device studies.

The investigator or designee must ensure that only patients 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. Able to understand and voluntarily sign the Informed Consent Form (ICF) and ability to comply with the study visit schedule and the other protocol requirements. Written informed consent must be obtained prior to any study specific procedures that are not part of standard of care. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.
2. Male or female patients must be ≥ 18 years of age.
3. Histologically or cytologically confirmed and documented stage IIIB, IIIC or IV (per American Joint Committee on Cancer (AJCC) staging system version 8), unresectable, squamous or non-squamous NSCLC which is in addition:
   a. harboring METΔex14 mutations, as determined by central pre-screening assessment performed at a Novartis designated laboratory, if not previously determined locally (only local assays agreed by Novartis will be accepted).
   b. Negative for any mutations that are known to sensitize to EGFR inhibitors, such as exon 19 deletions or L858R substitution
   c. Negative for ALK rearrangements

   Note: Patients with NSCLC of pure squamous cell histology can enter the study without EGFR mutation or ALK rearrangement testing or result; however, patients with pure squamous cell histology who are known to have EGFR mutations in exons 19 or 21 or ALK rearrangements will be excluded.

4. Have an archival tumor sample or newly obtained tumor biopsy.
   a. The archival samples must be most recently available FFPE block or cut tissue sections from the block.
   b. Patients must be suitable and willing to undergo study-required biopsies if there is no archival sample available.
5. Patients must not have received any systemic therapy for advanced/metastatic disease (stage IIIB, IIIC or IV NSCLC). Neo-adjuvant and adjuvant systemic therapies are permitted if relapse occurred > 12 months from the end of therapy.
6. At least one measurable lesion as defined by RECIST 1.1 as per investigator assessment.
7. Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (Common Terminology Criteria for Adverse Events [CTCAE] v 5.0). Patients with any grade of alopecia are allowed to enter the study.
8. Patients must have adequate organ function including the following laboratory values at the screening visit:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L without growth factor support
   - Platelets ≥75 x 10^9/L
   - Hemoglobin (Hgb) > 9 g/dL
   - Calculated creatinine clearance (using Cockcroft-Gault formula, see Appendix 4) ≥ 45 mL/min
   - Total bilirubin < 1.5 x Upper Limit of Normal (ULN)
   - Aspartate transaminase (AST) < 3 x ULN, except for patients with liver metastasis, who can be included if AST < 5 x ULN
   - Alanine transaminase (ALT) < 3 x ULN, except for patients with liver metastasis, who can be included if ALT < 5 x ULN
   - Alkaline phosphatase (ALP) < 5 x ULN
   - Asymptomatic serum amylase increased < grade 2. Patients with grade 1 or grade 2 serum amylase increased 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 < 1.5 x ULN
9. Eastern Cooperative Oncology Group (ECOG Performance Status (PS) of 0 or 1.
10. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.
11. **For subjects of Part 2 only**: Patients must have known PD-L1 tumor expression status as determined by IHC using the Dako PD-L1 IHC 22C3 pharmDx assay at a local laboratory or at a Novartis designated central laboratory.

5.2 Exclusion criteria

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

1. Prior treatment with a PD-1/PD-L1 inhibitor, MET inhibitor or HGF inhibitor.
2. Patients with 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).
3. 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.
4. Presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids 2 weeks prior to study entry. Patients with treated symptomatic brain metastases should be neurologically stable (for ≥ 4 weeks post-treatment and prior to study entry) and at a dose of ≤ 10 mg per day prednisone or equivalent for at least 2 weeks before administration of any study treatment.
5. Presence or history of carcinomatous meningitis.
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 criterion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
7. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
   - Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA Grade ≥ 2),
   - Acute myocardial infarction or unstable angina pectoris < 6 months prior to study entry
   - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.
   - Ventricular arrhythmias
   - Supraventricular and nodal arrhythmias not controlled with medication
   - Other cardiac arrhythmia not controlled with medication
   - QTcF ≥ 470 msec on the screening ECG (from mean of triplicate ECGs)
   - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
8. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤ 2 weeks prior to starting study treatment or patients who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment is allowed.

9. 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 will not be counted as major surgery and patients can start study treatment ≥ 1 week after the procedure.
10. Patients receiving:
    - strong inducers of CYP3A4 that cannot be discontinued at least 1 week prior to the start of study treatment and for the duration of the study,
    - medications with a "Known Risk of Torsades de Pointes" per www.qtdrugs.org that cannot be discontinued or replaced by safe alternative medication,
    - hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents in the last 2 weeks prior to start of study treatment. If thrombopoietin mimetics or erythroid stimulating agents were initiated more than 2 weeks prior to the first dose of study treatment and the patient is on a stable dose, they can be maintained.
    - live vaccines against infectious diseases within 4 weeks of initiation of study treatment.
    - systemic chronic steroid therapy (>10mg/day prednisone or equivalent) or any other immunosuppressive therapy within 7 days prior to planned date of first dose of study treatment. Note**:** Topical, inhaled, nasal and ophthalmic steroids are allowed.
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. Unable or unwilling to swallow tablets as per dosing schedule.
13. Active, known or suspected autoimmune disease or a documented history of autoimmune disease. Note: Patients with vitiligo, controlled type I diabetes mellitus on stable insulin dose, residual autoimmune-related hypothyroidism only requiring hormone replacement or psoriasis not requiring systemic treatment are permitted
14. History of allogenic bone marrow or solid organ transplant.
15. Presence or history of interstitial lung disease, non-infectious pneumonitis or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
16. Human Immunodeficiency Virus (HIV) infection. Note: Positive HIV test at screening where locally required.
17. Active HBV or HCV infection. Patients whose disease is controlled under antiviral therapy are eligible.
18. Any condition medical or psychotic conditions or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results.

19. Pregnant or nursing (lactating) women confirmed by a positive hCG laboratory test within 72 hours prior to initiating study treatment.

Note: Low levels of hCG may also be considered a tumor marker, therefore if low hCG levels are detected, another blood sample at least 4 days later must be taken to assess the kinetics of the increase and transvaginal ultrasound must be performed to rule out pregnancy.

20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 150 days after last dose of spartalizumab or placebo or for 7 days after last dose of capmatinib, whichever is longer. 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 six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
    - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal 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, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

21. Sexually active males unless they use a condom during intercourse while taking study treatment and for 7 days after stopping treatment and should not father a child in this period. A condom is required for all sexually active male participants to prevent them from fathering a child. In addition, male participants must not donate sperm for the time period specified above.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

6 Treatment

6.1 Study treatment

The investigational drugs to be used in this study are capmatinib and spartalizumab, as described in Table 6-1. The study treatment is defined as capmatinib plus spartalizumab or capmatinib plus placebo.

6.1.1 Investigational drugs

The treatment period begins on Cycle 1 Day 1. In other words, the first dose of study treatment (capmatinib plus spartalizumab or capmatinib plus placebo) is given on Day 1 of Cycle 1. The duration of each treatment cycle is 28 days.

Refer to Section 6.7.2 for study drug prescribing and administration information.

Spartalizumab will be supplied as concentrate for solution in open label vials and it will be diluted in dextrose 5% in water (D5W). Spartalizumab matching placebo will be D5W for infusion supplied by the site.

Table 6-1 Investigational drugs

Investigational Drugs Name and Strengths	Pharmaceutical Dosage Form	Route of Administration	Drug package	Supplier (global or local)	Dose and Regimen
Capmatinib (INC280) 150 mg or 200 mg	Film-coated tablet	Oral use	Open label, patient specific bottles	Global	400 mg BID
Spartalizumab (PDR001) 100 mg	Concentrate for solution for infusion	Intravenous use	Open label, patient specific vials	Global	400 mg Q4W

6.1.2 Additional study treatments

No other treatment beyond the investigational drugs described in Section 6.1.1 are included in this trial.

6.1.3 Treatment arms

Following the study enrollment halt, spartalizumab treatment has been discontinued and Part 2 will not be initiated.

Part 1: Single Arm Run-in Part

All eligible subjects enrolled in Part 1 will be treated with capmatinib 400 mg orally twice daily (BID) in combination with spartalizumab 400 mg iv every 28 days (Q4W).

A complete cycle of treatment is defined as 28 days of continuous capmatinib treatment and an infusion of spartalizumab every 28 days.

Part 2: Randomized Part

All eligible subjects enrolled in Part 2 will be assigned to one of the following treatment arms in a ratio of 2:1 according to stratification factors.

- Arm 1: capmatinib 400 mg orally twice daily (BID) plus spartalizumab 400 mg intravenously (iv) every 28 days (Q4W).
- Arm 2: capmatinib 400 mg orally twice daily (BID) plus spartalizumab matching placebo iv every 28 days (Q4W).

A complete cycle of treatment is defined as 28 days of continuous capmatinib treatment and an infusion of spartalizumab or placebo every 28 days.

6.1.4 Treatment duration

Subjects will be treated until they experience unacceptable toxicity, disease progression per RECIST 1.1 as determined by investigator assessment (with or without confirmation by BIRC), and/or treatment is discontinued at the discretion of the investigator or the subject. A complete list of the circumstances requiring study treatment discontinuation is provided in Section 9.1.1.

Subjects may continue treatment beyond disease progression if, in the judgment of the investigator, there is evidence of clinical benefit and the patient wishes to continue on the study treatment. Criteria for treatment beyond progression are described below.

Treatment beyond disease progression

Subjects will be permitted to continue study treatment beyond disease progression per RECIST 1.1 as determined by investigator, provided they meet all the following criteria:

- Clinical benefit per investigator's judgement
- 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

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

Subjects who meet the above criteria and continue study treatment beyond initial disease progression per RECIST 1.1 will continue all study procedures as outlined in Table 8-1b and Table 8-3.

In addition, subjects enrolled in Part 2, who continue study treatment beyond initial disease progression per RECIST 1.1 [redacted]. 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)

If a subject experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional practice at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional practice or the dose modification guideline (Section 6.5.1). In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a subject experiences a Grade ≥3 anaphylactic/anaphylactoid reaction, the subject will be discontinued from the study treatment.

The CTCAE category of "Infusion related reaction" should be used to describe study treatment related infusion reactions, unless the investigator considers another category, such as "Allergic reaction," "Anaphylaxis," or "Cytokine release syndrome" more appropriate in a specific situation.

6.2.1 Concomitant therapy

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

The subject must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications, food supplements and vitamins.

All medications (excluding the current study treatment), procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject signs the main study ICF and up to 30 days after the last dose of study drugs must be recorded in the appropriate eCRF.

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

Use of bisphonates or RANKL inhibitor

Treatment with bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor for pre-existing bone metastases is permitted, if clinically indicated and at the investigator's discretion following existing local guidelines. Treatment with bisphosphonates or RANKL inhibitor should preferably begin before the study treatment is initiated, but can also be initiated during therapy only if absence of radiological bone disease progression is well documented (in this case, the reason for its use must be clearly documented; i.e. "pre-existing, non-progressing, bone metastases").

Permitted radiotherapy

Localized radiotherapy for pre-existing, painful bone metastases is permitted. Local bone radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out. The study treatment must be interrupted on the days of radiotherapy and can be resumed the day after its completion. Caution is advised for radiation to fields that include lung tissue.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

6.2.1.1.1 Capmatinib

Permitted concomitant therapy requiring caution and/or action when co-administered with Capmatinib are as follows:

- **CYP1A2 substrates with narrow therapeutic index (NTI).**
  Capmatinib is a moderate CYP1A2 inhibitor. Co-administration of capmatinib increased sensitive CYP1A2 probe substrate (caffeine) AUC by 134%. CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions. If co-administration is unavoidable, decrease the CYP1A2 substrates dosage in accordance with the approved prescribing information.
- **Pgp or BCRP substrates.**
  Co-adminstration of capmatinib increased Pgp substrate (digoxin) exposure (AUC and Cmax by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUC and Cmax by 108% and 204%, respectively). Avoid co-administration of capmatinib with P-gp and BCRP substrates where minimal concentration changes may lead to serious adverse reactions. If co-administration is unavoidable, decrease the P-gp or BCRP substrates dosage in accordance with the approved prescribing information
- **Strong CYP3A4 inhibitors.**
  Co-administration of capmatinib with a strong CYP3A4 inhibitor (itraconazole) increased capmatinib AUC by 42%. There was no change in capmatinib Cmax. Closely monitor subjects for adverse reactions when using strong CYP3A4 inhibitors concurrently with capmatinib.

- **Moderate CYP3A4 inducers.**
  The effect of the moderate CYP3A4 inducer, efavirenz (600 mg once daily for 20 days) coadministered with capmatinib was simulated using the physiologically-based pharmacokinetic (PBPK) models. The models predicted a weak effect of 44% reduction in capmatinib AUC0-12 and 34% reduction in Cmax at steady state compared to administration of capmatinib alone. Caution should be exercised during concomitant use of capmatinib with moderate CYP3A inducers. Use an alternative medication with no or minimal potential to induce CYP3A during co-administration with capmatinib.
- **Proton Pump Inhibitors (PPIs).**
  Co-administration of capmatinib with proton pump inhibitor (rabeprazole) decreased capmatinib AUCinf by 25% and Cmax by 38%. Exercise caution during concomitant use of capmatinib with proton pump inhibitors.
- **Antacid and H2 receptor antagonists.**
  As an alternative to proton pump inhibitors, H2-receptor antagonist or antacid can be taken. 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 Appendix 3 for a list of the medications (presented by mechanism of interaction) that require caution when concomitantly used with capmatinib.

6.2.1.1.2 Spartalizumab

Hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents are allowed as per local or published guidelines; in case of anemia, thrombocytopenia or neutropenia, potential immune-mediated etiology should be ruled out.

Anticoagulation and anti-aggregation agents are permitted if the subjects are already at stable doses for > 2 weeks at time of first dose of spartalizumab/placebo, and International Normalized Ratio (INR) should be monitored as clinically indicated per investigator's discretion. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor sample according to the institutional guidelines.

Subjects with disease metastatic to bone may receive bone-stabilizing agents such as bisphosphonates or monoclonal antibodies intended for this purpose.

6.2.2 Prohibited medication

During the course of the study, subjects must not receive other antineoplastic therapies (e.g. investigational drugs, devices, chemotherapy, immunotherapies) or any other therapies that may be active against cancer or that are intended to modulate an immune response. However, limited-field palliative radiotherapy to non-target lesion(s) may be allowed as concomitant therapy upon discussion with the Novartis medical monitor. Such local therapies administered during the study treatment must be entered into the eCRF. The study treatment must be interrupted on the days of radiotherapy and can be resumed the day after its completion.

The use of live vaccines is not allowed during the study and up to 150 days from last dose of spartalizumab or 30 days from the last dose of capmatinib, whichever is longer.

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

6.2.2.1 Capmatinib: prohibited medication

Co-administration of capmatinib with a strong CYP3A4 inducer (rifampicin) decreased capmatinib AUC by 67% and Cmax by 56% (CINC280A2102), which may decrease capmatinib anti-tumor activity. Therefore concurrent use of strong CYP3A inducers is prohibited.

Capmatinib prohibited medications are listed in Appendix 3-Table 16-12.

6.2.2.2 Spartalizumab: prohibited medication

The use of systemic steroid therapy (at doses greater than 10 mg/day of prednisone or equivalent) and other immunosuppressive drugs is not allowed to subjects receiving spartalizumab, with the exception of:

- Topical, inhaled, nasal and ophthalmic steroids
- prophylactic use for subjects with imaging contrast dye allergy
- Replacement-dose steroids (defined as ≤10 mg/day of prednisone or equivalent dose of corticosteroids) in the setting of adrenal insufficiency.
- Transient exacerbations of other chronic inflammatory conditions, such as chronic obstructive pulmonary disease (COPD), requiring treatment. Steroids must be reduced to 10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next treatment with spartalizumab.
- Upon treatment of spartalizumab-related infusion reactions or spartalizumab-related irAEs, steroids must be reduced to ≤10 mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids prior to the next treatment with spartalizumab. Systemic corticosteroids must be tapered, and be at non-immunosuppressive doses, prior to the next administration of study treatment. If the dose of prednisone or equivalent cannot be reduced to < 10 mg/day before the administration of next dose of study treatment then spartalizumab/ placebo must be discontinued (note: next dose of spartalizumab/placebo can be delayed up to 12 weeks).

The use of live vaccines is not allowed from 4 weeks prior start of study treatment and up to 150 days from last dose of spartalizumab/placebo. Inactivated vaccines are allowed.

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 (either at pre-screening or screening) and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. A new subject number will be assigned at every subsequent enrollment if the subject is re-screened. 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

All subjects entering the main screening phase will be registered in the Interactive Response Technology (IRT) system. The investigator or his/her delegate will then contact the IRT once all the inclusion/exclusion criteria have been assessed to confirm whether the subject will start study treatment or not.

In Part 1, no randomization will be performed. All eligible subjects will be assigned to treatment with capmatinib plus spartalizumab.

In Part 2, all eligible subjects will be randomized via IRT in a 2:1 ratio to one of the following treatment arms:

- Arm 1: capmatinib plus spartalizumab
- Arm 2: capmatinib plus spartalizumab matching placebo

The randomization will be stratified by presence or absence of brain metastasis (as assessed by investigator per RECIST 1.1) and PD-L1 expression <1%, or 1-49%, or ≥50%) at baseline (either at pre-screening or screening).

The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify the investigational drugs to be dispensed to the subject.

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 the IRT provider 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, which in turn are linked to medication numbers. A separate medication list will be produced under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

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

6.4 Treatment blinding

Part 1: Single Arm Run-in Part

Not applicable. Treatment will be open to subjects, investigator staff, persons performing the assessments, and the clinical trial team (CTT).

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated.

The CTT will remain blinded to the identity of the treatment from the time of randomization until the reporting of primary PFS analysis. Subjects, investigator staff and persons performing the assessments will remain blinded to the identity of the treatment from the time of randomization until final lock of the study database, using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: unblinded Clinical Research Associates (CRAs), unblinded pharmacist/designee, independent statistician and programmer who will perform Data Monitoring Committee (DMC) analysis and the PK bioanalyst. These personnel will not be involved in any other trial activity and treatment allocation information will be kept confidential until the final database lock. The randomization codes will be disclosed to PK bioanalysts who will keep PK results confidential until the database is locked for primary PFS analysis. (2) The identity of the treatments (spartalizumab or placebo) will be concealed by the use of a non-translucent, opaque sleeve that will be placed on the infusion bag.

Open label or single blinded supply (spartalizumab and placebo) will be provided at sites to the unblinded site pharmacist.

IMPORTANT: Due to the difference in preparation methods between the active and placebo treatments, an unblinded pharmacist/designee who is independent of the investigational staff will be required. The unblinded pharmacist/designee will receive the appropriate treatment allocations. Appropriate measures must be taken by the unblinded pharmacist to ensure that the investigational staff remains blinded throughout the study. The unblinded pharmacist must not administer the drug to the subject nor have any contact with the study participants. Please refer to the Pharmacist Instruction Manual.

An independent statistical group (external to and independent of Novartis), not involved in the trial conduct, will prepare semi blinded data reports for the DMC. Details will be presented in the DMC charter.

Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of subjects. Unblinding will only occur in the case of subject emergencies (see Section 6.6.2), following the DMC recommendations (e.g. after the interim analyses, see Section 12.7), for regulatory reporting purposes or at the end of the study. Except in these cases, documented approval by the Novartis study physician is required prior to unblinding a subject's treatment assignment. In case of unblinding, all data is required to be captured in the eCRF prior to unblinding. Data after unblinding will continue to be collected as per protocol. The date of any unblinding and the reason will also be collected.

In rare cases when unblinding occurs because of emergency subject management, the actual treatment arm will not be communicated to any of the Novartis employees involved in running the trial in order to remain blinded.

6.5 Dose modification

6.5.1 Dose modification

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

The following guidelines should be considered:

- Dose reductions are not permitted for spartalizumab/.
- Dose reductions are allowed for capmatinib and should follow the dose reduction steps described in Table 6-2. For each subject, a maximum of two dose level modifications is allowed after which the subject must be discontinued. Dose reductions of capmatinib below 200 mg BID are not permitted.
- Dose re-escalation of capmatinib to the previous dose level is allowed only once, and if no AE leading to dose modification is observed after at least 1 cycle (4 weeks) of study treatment at the reduced dose.
- Dose interruptions due to toxicities are permitted for both spartalizumab and capmatinib. Dosing of capmatinib may resume once the adverse event has resolved, as described in Table 6-3. All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity graded according to CTCAE v5.0 (http://ctep.cancer.gov).
- For clinical management of suspected immune-related events, 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 clinical practice guideline for Management of Immune-Related Adverse Events in Patients 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). Note that in general, study treatment should be interrupted for grade 3 and 4 toxicities and for a subset of lower grade toxicities.
- 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.
- Overall, for adverse events of potential immune-related etiology (irAE) that do not recover to the extent required in the Table 6-3 at a dose of immunosuppression of ≤ 10 mg/day prednisone or equivalent and/or requiring continuation of other immunosuppressive drugs within 12 weeks after initiation of immunosuppressive therapy, spartalizumab/placebo must be permanently discontinued.
- If, due to study drug related toxicity, a subject requires to interrupt capmatinib for > 3 weeks, then the subject should be discontinued from study treatment. Exceptions to this requirement may be permitted following documented discussion with the Novartis medical monitor.
- Treatment continuation with spartalizumab alone is not permitted.

- All interruptions or change to study drug administration must be recorded on the Dose Administration Record eCRF.

Table 6-2 Dose reduction steps for capmatinib

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

Table 6-3 Dose modifications of capmatinib and spartalizumab/placebo and recommended clinical management for Adverse Events

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Infusion related reaction or hypersensitivity reaction - Note: no action required with capmatinib treatment		
Grade 1	Decrease spartalizumab/placebo infusion rate until recovery from the symptoms.	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.
Grade 2	Stop spartalizumab/placebo infusion immediately, and keep line open. If symptoms resolve, restart infusion at 50% of previous rate under continuous observation. If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then permanently discontinue spartalizumab/placebo treatment.	1. Stop Infusion 2. Treat as per local institutional guidelines, which may include: i.v. fluids, antihistamines, NSAIDS, acetaminophen, narcotics, oxygen and corticosteroids as indicated 3. Increase monitoring of vital signs/pulse oximetry as medically indicated until patient is deemed medically stable If symptoms resolve, the infusion may be restarted at 50% of the original infusion rate. 4. Premedicate patient ~ 1.5h prior to next infusion of spartalizumab/placebo with: ● Diphenhydramine 50 mg po (or equivalent dose of antihistamine). ● Acetaminophen 500-1000 mg po (or equivalent dose of analgesic). ● Or as per local institutional guidelines
Grade ≥3	Stop spartalizumab/placebo infusion immediately, and discontinue spartalizumab/placebo treatment permanently.	1. Stop Infusion 2. Treat as per local institutional guidelines, which may include: iv fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, corticosteroids, epinephrine 3. Close monitoring of vital signs, pulse oximetry and ECG as medically indicated until the patient is deemed medically stable 4. Hospitalization may be indicated.
Fatigue		
Grade ≥3	Hold study treatment. Upon resolution to ≤ Grade 1 within ≤ 7 days, resume study treatment without dose modification, If resolved in > 7 days, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level.	Treat per local/institutional guidelines

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Peripheral edema (generalized edema or localized edema)		
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level.	Consider conservative measures such as leg elevation, compression stockings and dietary salt modification as clinically indicated and treat per local/institutional guidelines
Grade 4	Discontinue study treatment.	Intensify as above and treat per local/institutional guidelines
Ocular (uveitis, eye pain, blurred vision) - Note: no action required with capmatinib treatment		
Grade 2	Hold spartalizumab/placebo treatment. Upon resolution to ≤ Grade 1 may consider resuming spartalizumab/placebo treatment at same dose level.	Consult with ophthalmologist
Grade ≥3	Discontinue spartalizumab/placebo treatment.	
Pneumonitis/ILD – Note: subjects on combination therapy with capmatinib and spartalizumab/placebo should be monitored for pulmonary symptoms indicative of ILD/pneumonitis.		
Grade 1	Hold study treatment and perform diagnostic workup for ILD/Pneumonitis. If ILD/Pneumonitis is confirmed, discontinue study treatment. If ILD/Pneumonitis is not confirmed, upon resolution resume study treatment without dose modifications, At second occurrence, discontinue study treatment.	1. Exclude infections or other etiologies 2. CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression re-image at least every 3 weeks 3. Monitor for symptoms every 2-3 days 4. Clinical evaluation and laboratory work-up for infection 5. Monitoring of oxygenation via pulse oximetry recommended 6. Consultation with pulmonologist recommended

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Grade 2	Mandatory: hold study treatment until improvement to ≤ Grade 1 and perform diagnostic workup for ILD. If ILD/Pneumonitis is confirmed, discontinue study treatment. If ILD/Pneumonitis is not confirmed, study treatment may be resumed as follows: • If resolved to ≤ Grade 1 within ≤ 7 days, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level • If resolved in > 7 days, or at second occurrence after capmatinib dose reduction, discontinue study treatment.	1. Exclude infections or other etiologies 2. CT scan (high-resolution with lung windows) 3. Monitor symptoms daily, consider hospitalization 4. Clinical evaluation and laboratory work up for infection 5. Consult pulmonologist 6. Pulmonary function tests - if normal at baseline, repeat every 8 weeks 7. Bronchoscopy with biopsy and/or BAL recommended 8. Symptomatic therapy including corticosteroids [c] if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated). 9. Consider empirical antibiotics 10. If no improvement within 2-3 days, or worsening, treat as grade 3
Grade ≥ 3	Mandatory: Discontinue study treatment	1. CT scan (high-resolution with lung windows) 2. Hospitalization and pulmonary and infectious disease consultation 3. Clinical evaluation and laboratory work-up for infection 4. Commence oxygen therapy 5. Consult pulmonologist 6. Pulmonary function tests*. If < normal, repeat every 8 weeks until ≥ normal 7. Bronchoscopy** with biopsy and/or BAL if possible 8. Treat with iv steroids*** (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, switch to high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) then slow taper over ≥4-6 weeks 9. If iv steroids followed by high dose oral steroids do not reduce initial symptoms within 48 consider non-corticosteroid immunosuppressive medication 10 Empiric antibiotics

* 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.
** 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.
*** Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. Consider tapering dosage at end.

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
ECG QTc-Interval prolonged		
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 2 within ≤ 7 days, resume study treatment without dose modification, If resolved in > 7 days, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level.	1. Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. 2. Review concomitant medication usage for the potential to inhibit CYP3A4/5 and/or to prolong the QT-interval 3. Check compliance with correct dose and administration of capmatinib. 4. Repeat ECG within one hour of the first QTcF of ≥501 ms. 5. If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once daily until the QTcF returns to < 501 ms. 6. 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 subject with QTcF prolongation should be maintained on study.
Grade 4	Discontinue study treatment.	As for Grade 3
Myocarditis		
Myocarditis grade ≥2 or other cardiac event grade ≥3	Mandatory: permanently discontinue study treatment	Ensure adequate evaluation to confirm etiology and/or exclude other causes. Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d Consult with specialist; hospitalization as indicated

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Diarrhea/colitis		
Grade 1	May continue study treatment.	Treat symptoms (loperamide*, hydration, diet) and monitor closely
Grade 2 (despite appropriate anti-diarrheal medication)	Hold study treatment. Upon resolution to ≤ Grade 1 resume study treatment without dose modification, At second occurrence of ≥ Grade 2, hold study treatment until resolved to ≤ Grade 1, then reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level	1. Consult with GI specialist 2. Stool evaluation, imaging and endoscopy as clinically indicated 3. Symptomatic treatment (loperamide*, hydration, diet). 4. If considered immune-related commence steroids (0.5-1 mg/kg/d prednisone or IV equivalent) until recovery to Grade 1, particularly in case of persisting/worsening symptoms, ulcerations or bleeding seen on endoscopy, or blood in stool. If no improvement within few days, manage as per Grade 3. 5. Slowly taper steroids once symptoms improve to Grade 1 (i.e. over 4-6 weeks)
Grade 3 or (despite appropriate anti-diarrheal medication)	Hold study treatment. Upon resolution to ≤ Grade 1 of diarrhea, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level. At second occurrence of ≥ Grade 3, discontinue study treatment.	1. Consider hospitalization; rule out bowel perforation and initiate IV hydration as needed 2. Consultation with GI specialist; consider endoscopy and biopsy 3. If considered immune-related, in addition to symptomatic treatment initial treatment with IV steroids (1 to 2 mg/kg/d of methylprednisolone or equivalent) 4. Consider antibiotics as appropriate 5. If no improvement in 2-3 days: consider initiating infliximab 5 mg/kg and continue steroids. (infliximab is contraindicated in patients with sepsis/perforation) 6. Slowly taper steroids once symptoms improve to Grade 1 (4 to 6 weeks) 7. If symptoms worsen during steroid reduction, re-escalate as needed followed by more prolonged taper and consider infliximab
Grade 4	Discontinue study treatment	Urgent hospitalization, supportive care and specialist consultation as outlined for Grade 3 toxicity

*Loperamide exposure may be increased in the presence of capmatinib, subjects receiving this treatment should be closely followed. For **diarrhea suspected to be related to capmatinib**, treatment with steroids and/or infliximab is not indicated. For complicated diarrhea associated with capmatinib (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. Note: complicating signs or symptoms include moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration.

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Vomiting		
Grade 1 (despite appropriate anti-emetics)	Continue study treatment.	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. Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator`s best judgement*..
Grade ≥3 (despite appropriate anti-emetics)	Hold study treatment. Upon resolution to ≤ Grade 1, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at the same dose level.	Treat per local/institutional guidelines
*Aprepitant exposure may be increased in the presence of capmatinib, subjects receiving this treatment should be closely followed.		
Nausea		
Grade 3 (despite appropriate anti-emetics)	Hold study treatment. Upon resolution to ≤ Grade 1, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at the same dose level.	Treat per local/institutional guidelines

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
AST and/or ALT increased		
Grade 2 AST and/or ALT	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1 or baseline, consider resuming study treatment without dose modification.	Monitor hepatic laboratory tests more frequently (every 2-3 days) until resolved to ≤ grade 1 Rule-out alternative causes (e.g. concomitant medications, infection, disease progression) Consider prednisone (0.5-1 mg/kg/d) if liver tests worsen and/or significant symptoms
Grade 3 AST and/or ALT	Hold capmatinib treatment. Permanently discontinue spartalizumab/placebo Upon resolution to ≤ Grade 1 or baseline within ≤ 7 days, resume capmatinib treatment without dose modification If resolved in > 7 days, reduce capmatinib ↓ 1 dose level.	1. Monitor hepatic laboratory more frequently (every 2-3 days) until returned to ≤ grade 1. 2. Consult with hepatologist; consider hospitalization and liver biopsy to establish etiology 3. Initiate treatment with steroids (prednisone 1-2 mg/kg/d or IV equivalent) 4. Add prophylactic antibiotics for opportunistic infections as appropriate 5. Once symptoms/liver tests improve to Grade ≤1, taper steroids over at least 4 weeks 6. If no improvement or steroid refractory after 3 days, consider oral mycophenolate as per local treatment guidance 7. Infliximab is not recommended due to its potential for hepatotoxicity
Grade 4 AST and/or ALT	Mandatory: permanently discontinue study treatment.	As for Grade 3 toxicity above

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Isolated total bilirubin increased		
Grade 2	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline within ≤ 7 days, resume study treatment without dose modification, If resolved in > 7 days, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level.	Frequent monitoring of Liver Function Tests (LFTs), (every 2-3 days) until resolved to ≤ grade 1 Rule-out alternative causes (e.g. concomitant medications, infection, disease progression)
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level. If resolved in > 7 days, discontinue study treatment.	Frequent monitoring of LFTs, (every 2-3 days), until resolved to ≤ grade 1. 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
Grade 4	Mandatory: Discontinue study treatment.	After permanently discontinuing the subject from study treatment, the subject should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to ≤ grade 1 or stabilization over 4 weeks.
Combined elevations of AST or ALT and Total Bilirubin		
Grade 2 AST and/or ALT with bilirubin ≥Grade 2 (unless Gilbert's syndrome) OR For participants with elevated baseline AST or ALT or total bilirubin value: [AST or ALT > 3 x baseline] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN] without evidence of cholestasis or hemolysis	Mandatory: discontinue study treatment.	After permanently discontinuing the subject from study treatment, 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 grade 1 or stabilization over 4 weeks

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Amylase and/or lipase increased		
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 14 days, resume study treatment without dose modification, If resolved in > 14 days, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level.	Perform CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within one week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase elevation
Grade 4	Discontinue study treatment	
Pancreatitis		
Grade 2/radiologic evidence	Hold study treatment. Upon resolution, may resume study treatment without dose modification	Evaluate for pancreatitis (clinical assessment, abdominal imaging and/or MRCP as appropriate) Initiate steroids in case of ≥ grade 2 acute pancreatitis
Grade ≥3	Mandatory: discontinue study treatment.	As for Grade 2
Creatinine increased, nephritis		
Grade 1	Continue study treatment	Monitor creatinine weekly Rule-out other causes (e.g. fluids, medications, IV contrast) Promote hydration and consider cessation of nephrotoxic drugs
Grade 2	Hold study treatment. Upon resolution to ≤ Grade 1, resume study treatment without dose modification	1. Monitor creatinine every 2 to 3 days 2. Initiate 0.5 to 1 mg/kg/day prednisone or equivalents if other causes are ruled-out 3. If worsening or no improvement: 1 to 2 mg/kg/day prednisone or equivalents 4. Promote hydration and cessation of nephrotoxic drugs 5. Consult with specialist and consider renal biopsy Rule-out other causes (e.g. fluids, medications, IV contrast) If worsening or no improvement: 1 to 2 mg/kg/d prednisone or equivalents
Grade 3	Upon resolution to Grade ≤ 1, reduce capmatinib ↓ 1 dose level and discontinue spartalizumab/placebo.	1. Monitor creatinine every 1 to 2 days 2. Start 1 to 2 mg/kg/day prednisone or equivalents. Once event improves to Grade ≤1, slowly taper steroids over at least 4-6 weeks 3. Promote hydration and cessation of nephrotoxic drugs 4. Consult with specialist and consider renal biopsy

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Grade 4	Discontinue study treatment.	As for Grade 3 toxicity
Immune-related endocrinopathies (e.g. hypophysitis, adrenal insufficiency, hyperthyroidism or hypothyroidism) - Note: no action required with capmatinib treatment		
Asymptomatic, intervention not indicated	Continue study treatment	If Thyroid Stimulating Hormone (TSH) <0.5x LLN, or TSH >2x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated Consider endocrinologist consult If hypophysitis is suspected, consider pituitary gland imaging (MRIs with gadolinium and sellar cuts); evaluate hormone levels as clinically indicated Repeat labs in 1 to 3 weeks/MRI in 1 month if laboratory abnormalities persist but normal lab/pituitary scan
Symptomatic	Hold spartalizumab/placebo until recovery to mild or no symptoms, and controlled with hormone replacement therapy Hypothyroidism may be managed with replacement therapy without treatment interruption (unless life-threatening) Permanently discontinue spartalizumab/placebo for life-threatening endocrinopathies (i.e. hyperthyroidism, adrenal insufficiency, hypophysitis) or recurring severe/life-threatening events not controlled by hormone replacement therapy.	Endocrinology consultation Rule out infection/sepsis and other alternative causes with appropriate cultures/imaging Evaluate hormone levels (e.g. ACTH, cortisol FSH/FH, TSH, free T4, testosterone/estrogen), metabolic panel (e.g. Na, K, CO2, glucose), and imaging (e.g. brain MRI) as clinically indicated Initiate hormone replacement therapy as appropriate Consider steroids (methylprednisolone 1 to 2 mg/kg/d or equivalent) in case of severe hypophysitis or thyrotoxicosis Consider beta-blocker in case of severe hyper-thyroidism Consider hospitalization (e.g. in case of severe adrenal insufficiency/crisis), fluid replacement, and other supportive measures as clinically indicated

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Autoimmune diabetes - Note: no action required with capmatinib treatment		
Grade 3 or symptomatic hyperglycemia	Hold spartalizumab/placebo until recovery to ≤ Grade 1 or baseline Permanently discontinue spartalizumab/placebo in case of recurring severe/life-threatening events not controlled by anti-glycemic therapy.	Initiate anti-glycemic therapy (i.e. insulin) as medically indicated Monitor glucose levels regularly until metabolic control is achieved
Grade 4 hyperglycemia or life-threatening complications	Hold spartalizumab/placebo until recovery to grade 1 or baseline Permanently discontinue spartalizumab/placebo in case of recurring severe/life-threatening events not controlled by anti-glycemic therapy.	Initiate anti-glycemic therapy (i.e. insulin) as medically indicated Monitor glucose levels regularly until metabolic control is achieved Consider endocrinology consultation Evaluate for ketoacidosis as medically indicated Consider hospitalization (e.g. in case of ketoacidosis)
Encephalitis or aseptic meningitis - Note: no action required with capmatinib treatment		
	Discontinue spartalizumab/placebo	Rule out infectious or other causes of moderate to severe neurologic deterioration, and consult with specialist. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents.
Guillain-Barre Syndrome, severe peripheral or autonomic neuropathy, or transverse myelitis - Note: no action required with capmatinib treatment		
	Discontinue spartalizumab/placebo	Hospitalization and consult with specialist
Other immune-related neuropathies (e.g. autoimmune neuropathy, demyelinating polyneuropathy, etc.) - Note: no action required with capmatinib treatment		
Grade 1	Continue study treatment	Provide symptomatic treatment evaluate/monitor adequately
Grade 2	Consider holding spartalizumab/placebo treatment until recovery to ≤ Grade 1 or baseline	Ensure adequate evaluation to confirm etiology or exclude other causes Provide symptomatic treatment Systemic corticosteroids may be indicated Consider biopsy or additional tests for confirmation of diagnosis A specialist should be consulted
Grade 3	Hold spartalizumab/placebo until recovery to ≤ Grade 1 or baseline May restart spartalizumab/placebo treatment at the same dose and schedule taking into account the risks and benefits	Initiate systemic corticosteroids (prednisone at a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate Monitor closely and consult with a specialist

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Grade 4	Discontinue spartalizumab/placebo	Hospitalization and consult with specialist Initiate systemic corticosteroids (prednisone a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate
Myasthenia gravis - Note: no action required with capmatinib treatment		
Grade 2	Hold spartalizumab/placebo until recovery to ≤ Grade 1 or baseline	Consult with specialist Consider pyridostigmine and systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d; other therapies as appropriate (e.g. IVIG) Hospitalization in case of severe cases
Grade ≥3	Discontinue spartalizumab/placebo	
Rash/Photosensitivity – Note: 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).		
Grade 1	Continue study treatment without dose modification.	1. Initiate prophylactic and symptomatic treatment measures. 2. Consider use of antihistamines and /or topical corticosteroids or urea containing creams in combination with oral antipruritics or moderate strength topical steroid (hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) 3. Reassess after 2 weeks
Grade 2	Consider holding spartalizumab/placebo and continue capmatinib treatment Upon resolution to ≤ Grade 1, resume spartalizumab/placebo treatment without dose modification. In case of bullous dermatitis, acute generalized exanthematous pustulosis or DRESS, hold spartalizumab/placebo treatment until recovery to Grade ≤1 or baseline	1. Consider to initiate systemic steroids (e.g. oral prednisolone 0.5-1mg/kg daily). In addition, treat with topical emollients, oral antihistamines, and medium/high-potency topical steroids 2. If symptoms persist or recur consider skin biopsy.
Grade 3	Hold study treatment. Upon resolution to Grade 1, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level. If resolved in > 7 days, discontinue study treatment. For patients with severe cutaneous adverse reaction or bullous dermatitis, risk/benefit should be carefully considered before resuming spartalizumab/placebo treatment.	1. Consult with dermatologist and consider skin biopsy. 2. Initiate systemic steroids (1 mg/kg/d prednisone or IV equivalent); consider increasing if no improvement 3. High-potency topical steroids 4. Topical emollients, oral antihistamines as indicated 5. Consider GABA agonists or aprepitant in case of severe pruritus

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Grade 4	Discontinue study treatment	Urgent dermatologic consultation and additional measures as per local guidelines
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Discontinue study treatment	Hospitalization and urgent dermatology consultation Institute supportive care immediately as per local/institutional guidelines
Neutrophil count decreased		
Grade ≥3	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification, If resolved in > 7 days, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level.	Treat per local/institutional guidelines
Febrile neutropenia		
Grade ≥3	Hold study treatment. Upon resolution within ≤ 7 days, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level, If resolved in > 7 days, permanently discontinue study treatment	Treat per local/institutional guidelines
Platelets count decreased		
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 2 within ≤ 7 days, resume study treatment without dose modification. If resolved in > 7 days, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level.	Treat per local/institutional guidelines
Grade 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline, reduce capmatinib ↓ 1 dose level.	Treat per local/institutional guidelines

Worst toxicity CTCAE grade	Dose Modification	Recommended Clinical Management
Anemia		
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification. If resolved in > 7 days, reduce capmatinib ↓ 1 dose level, and resume spartalizumab/placebo at same dose level.	Treat per local/institutional guidelines
Grade 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level. At second occurrence, permanently discontinue study treatment.	Treat per local/institutional guidelines
Autoimmune hemolytic anemia, hemolytic uremic syndrome, or acquired hemophilia grade ≥ 3	Discontinue spartalizumab/placebo	Consult with specialist Consider systemic corticosteroids and other therapies as appropriate (e.g. transfusion) per local institutional guidelines local institutional guidelines
Other adverse events		
Grade 1 or 2	Maintain dose level, initiate supportive treatment as clinically indicated. For any intolerable grade 2 (e.g. limiting instrumental ADL), consider omitting the dose until resolved to ≤ grade 1, then then restart either at same dose or ↓ 1 dose level.	
Grade 3	Omit dose until resolved to ≤ grade 1, then↓ 1 dose level	
Grade 4	Permanently discontinue capmatinib	
Note: All dose modifications should be based on the worst preceding toxicity.		

6.5.2 Follow-up for toxicities

All subjects will be followed for safety up to 150 days after last dose of spartalizumab/placebo or 30 days after the last dose of capmatinib, whichever is longer. For subjects who are transferred to another clinical study or alternative treatment option to continue capmatinib treatment at end of study, no further safety data will be collected as part of this study (for details, please refer to Section 9.2.1).

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 described in Table 6-3 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.

The emergence of irAE may be anticipated in subjects receiving spartalizumab 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 to verify the immune-related nature of the AE and to exclude alternative explanations. Recommendations (Section 6.5.1) have been developed to assist investigators in assessing and managing the most frequently occurring irAEs.

Patients whose treatment is interrupted or permanently discontinued due to an irAE, AE 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 30 days, and subsequently at approximately 30-day intervals (or more frequently if required by institutional practices, or if clinically indicated), until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

If an AE is suspected to be immune-related the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed. All subjects receiving spartalizumab/placebo must be followed for irAEs, AEs and SAEs for 150 days after the last dose of study treatment. Please refer to Section 10 for additional details.

Recommendations for follow-up evaluations of selected toxicities are reported in Table 6-3.

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

Subjects with transaminase increase combined with total bilirubin (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 x ULN combined with TBIL > 2.0 x ULN

- For sub7jects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

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

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

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

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

Perform relevant examinations (Ultrasound or MRI, ERCP) as appropriate, to rule out an extrahepatic cause of cholestasis (cholestasis is defined as ALP elevation > 2.0 x ULN with R value < 2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (livertox.nih.gov/rucam.html).

Table 6-4 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-4 Clinical and diagnostic assessments for LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Ceruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Other causes should also be considered based upon subjects' medical history (hyperthyroidism/ thyrotoxic hepatitis – T3, T4, TSH; CVD / ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

Obtain PK sample to determine exposure to study treatment.

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

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

The IRT system will be contacted at each study treatment administration/dispensation. Additional details are provided in IRT manual.

The investigator must promote compliance by instructing the subject to take the study treatment 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 the study treatment as prescribed. All dosages prescribed to the patient and all dose changes, interruptions during the study must be recorded on the Dosage Administration Record eCRFs.

Compliance to capmatinib will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the subject.

All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all treated subjects as detailed in Section 8.5.2.

6.6.2 Emergency breaking of assigned treatment code

Part 1: Single Arm Run-in Part

Not applicable.

Part 2: Randomized Part

Following the study enrollment halt, Part 2 will not be initiated.

Emergency code breaks (unblinding decisions) must only be undertaken in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible

treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Blinding codes may also be broken after a subject discontinues treatment due to disease progression if deemed essential to allow the investigator to select the patient's next treatment regimen, and after discussion and agreement with the sponsor. Emergency treatment code breaks are performed using the IRT.

When the investigator/designee contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator/designee will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- subject number

In addition, the investigator must provide oral and written information to the subject on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Except for medical emergencies, for regulatory reporting purposes, or if it is critical to determine subsequent therapy after disease progression, documented approval by the Novartis study physician is required prior to unblinding a subject's treatment assignment.

Study treatment must be discontinued once emergency unblinding has occurred. If a subject is unblinded, he/she must be discontinued from the study treatment and must be followed for efficacy and survival, as applicable per Section 9.2.2.

6.7 Preparation and dispensation

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

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

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

Note: To maintain the blind in Part 2, study drugs will be kept in a location to which only the unblinded pharmacist, unblinded CRA, or unblinded designated staff have access, the investigational treatments will be prepared by an unblinded pharmacist/designee, and the bags will be covered by a non-translucent, opaque sleeve. Only study personnel blinded to treatment allocation must administer spartalizumab or placebo.

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. 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.

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

6.7.2 Instruction for prescribing and taking study treatment

Following the study enrollment halt, spartalizumab treatment has been discontinued in all ongoing subjects.

The dose and treatment schedule of each investigational drug used in this study is described in Table 6-5.

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

Table 6-5 Dose and treatment schedule

Investigational Drugs	Dose	Frequency and/or Regimen
Capmatinib (INC280) 150 mg or 200 mg	400 mg p.o. (2 x 200 mg) OR 300 mg p.o. (2 x 150 mg) if dose level -1 is required OR 200 mg p.o. (1 x 200 mg) if dose level -2 is required	Twice daily (28 days cycle)
Spartalizumab (PDR001) 100 mg	400 mg i.v. (4 x 100 mg vials*)	Once every 28 days
* A higher number of vials might be required if closed system drug-transfer devices (CSTDs) are used, for more details please refer to the Study Pharmacy manual.		

6.7.2.1 Capmatinib

Capmatinib tablets will be administered orally on a continuous twice daily (BID) dosing schedule, from Day 1 till Day 28 of each 28 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. A complete cycle of treatment is defined as 28 days of twice daily treatment with capmatinib. The investigator must instruct the subject to take the study drug exactly as prescribed.

- Subjects should take capmatinib tablets BID at approximately the same time each day starting on Cycle 1 Day 1.
- Each dose of capmatinib is to be taken with a glass of water (at least 8 ounces – approximately 250 mL) and consumed over as short a time as possible (i.e. not slower than approximately 1 tablet every 2 minutes).
- Subjects should be instructed to swallow the whole tablets and not to chew them.
- Capmatinib can be administered with or without food. The morning and the evening doses should be taken 12 (± 4) hours apart, although a 12-hour interval is highly recommended. The morning dose should be taken at the same time each morning. If a dose is not taken within 4 hours of the planned dosing time, the missed dose should not be replaced.
- On days of co-administration of capmatinib with spartalizumab, subjects should be instructed to take the morning dose of capmatinib during the clinic visit, when instructed by site personnel. Capmatinib will be administered prior to spartalizumab/placebo infusion along with its pre-medication (if pre-medication is necessary).
- On days when PK blood samples are to be collected, subjects will be instructed to hold their dose until arrival at the study center. The pre-dose PK samples will be taken right before capmatinib administration. The exact time of drug administration should be recorded in the eCRF. If a subject vomits within 4 hours of capmatinib dosing, the time of vomiting will also be recorded in the eCRF.
- Subjects should be instructed not to make up for missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined when the full dose is not taken within 4 hours of the scheduled twice daily dosing. If that occurs, then the dose (or part of the remaining dose) should not be taken and dosing should restart with the next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose.
- During the whole duration of treatment with capmatinib, the subject is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, avoid sunbathing or using a solarium).

6.7.2.2 Spartalizumab/placebo

Spartalizumab will be supplied in a vial as concentrate for solution for infusion. Spartalizumab (liquid) will be diluted in dextrose 5% in water (D5W). Due to incompatibility, 0.9% sodium chloride must not be used. Spartalizumab matching placebo will be a Dextrose 5% in water (D5W) infusion supplied by the site.

Spartalizumab/placebo will be administered intravenously as a 30 minutes infusion (up to 2 hours, if clinically indicated). Infusion must take place in a facility with appropriate resuscitation equipment available at the bedside, and a physician readily available during the period of drug administration.

Subjects should be closely observed for potential infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever, and vital signs monitored more frequently if clinically indicated, during and for at least 2 hours after the first two spartalizumab infusions. The same may apply for the subsequent spartalizumab infusions if medically indicated. Subjects should be further provided instructions to notify study personnel if symptoms of infusion reaction occur after any spartalizumab infusion.

Further instructions for the preparation and dispensation of spartalizumab are described in the Study Pharmacy Manual.

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). 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 capmatinib and spartalizumab can be found in their respective Investigator's Brochure (IB). 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 Investigator’s Brochure 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.

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.

[redacted]

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

As per Section 4.6, during a public health emergency as declared by local or regional authorities, e.g., 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 local Health 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 subject and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1b for Part 1, Table 8-2 for Part 2) lists all 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 8-1b or 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.

As per Section 4.6, during a public health emergency as declared by local or regional authorities, e.g., 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 ditactes. If allowed by the local Health Authority and dependent on operational capabilities, phone calls, virtual contacts (e.g. teleconsult) can replace on-site study visits, during the disruption until it is safe for the subject to visit the site again.

The following time windows are allowed per protocol:

- -28 days to -1 day from start of study treatment (Part 1) or from randomization (Part 2) for screening procedures
- Laboratory assessments performed as part of the screening evaluations that are within 72 hours of the first dose of study treatment are not required to be repeated on the first day of dosing (cycle 1 day 1)

- ±3 days for on treatment visits and assessments
- ±7 days for the 30 days safety follow up visit
- ±14 days for 60-, 90-, 120-, 150- safety follow up visits/calls
- For imaging evaluations a ± 7 days window is allowed.

Table 8-1 Assessment Schedule - Part 1 (Single Arm Run-in Part) – obsolete upon approval of protocol amendment 01

Period	**Screening**		**Treatment**												**Post treatment follow-up**					
Visit Name	**Molecular pre-screening**	**Main screening**	**C1**		**C2**	**C3**				**C4**	**C5**	**C6**	**Subsequent cycles**	**EOT**	**Safety Follow-up**					**Survival Follow-up**
															30 day	**60 day**	**90 day**	**120 day**	**150 day**	
Days		**-28 to -1**	**D1**	**D15**	**D1**	**D1**	**D4**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**		**-**	**-**	**-**	**-**	**-**	**every 12 weeks**
Informed consent for molecular pre-screening	X																			
Confirmation of EGFR wt and ALK rearrangement negative status (local data)	X																			
Collection of archival tumor sample or newly obtained tumor sample for central MET testing (if no local data available)	X																			
Informed consent		X																		
MET mutation status (result of central testing or local data if available)	X																			
Collection of archival tumor sample or newly obtained tumor sample		X				X (any day from C3D1 to C3D15)								X (Optional)						
Inclusion / Exclusion criteria		X																		
Demography	X																			
[redacted]																				

Period	Screening		Treatment												Post treatment follow-up					
Visit Name	Molecular pre-screening	Main screening	C1		C2	C3				C4	C5	C6	Subsequent cycles	EOT	Safety Follow-up					Survival Follow-up
															30 day	60 day	90 day	120 day	150 day	
Days		-28 to -1	D1	D15	D1	D1	D4	D8	D15	D1	D1	D1	D1		-	-	-	-	-	every 12 weeks
[redacted]																				
Smoking history		X																		
Diagnosis and extent of cancer		X																		
Prior antineoplastic therapy (meds, surgery, radiation)		X																		
Relevant medical history/current medical conditions		X																		
Concomitant medications		X (from screening up to 150 days from last dose of spartalizumab or 30 days from last dose of capmatinib whichever is longer or start of new anti-neoplastic therapy)																		
Adverse Events		X (from screening up to 150 days from last dose of spartalizumab or 30 days from last dose of capmatinib whichever is longer, after start of new anti-neoplastic therapy only suspected AEs will be collected). For SAE reporting please refer to Section 10.																		
Physical Examination		S	S	S	S	S				S	S	S	S	S						
Height		X																		
Weight		X	X		X	X				X	X	X	X	X						
Vital signs		X	X	X	X	X				X	X	X	X	X						
Performance status		X	X		X	X				X	X	X	X	X						
Hematology		X	X	X	X	X				X	X	X	X	X						
Chemistry		X	X	X	X	X				X	X	X	X	X						
Urinalysis		S	S (if clinically indicated)																	

Period	Screening		Treatment											Post treatment follow-up					
Visit Name	Molecular pre-screening	Main screening	C1		C2	C3				C4	C5	C6	Subsequent cycles	EOT	Safety Follow-up					Survival Follow-up
															30 day	60 day	90 day	120 day	150 day	
Days		-28 to -1	D1	D15	D1	D1	D4	D8	D15	D1	D1	D1	D1		-	-	-	-	-	every 12 weeks
Coagulation		X	X (if clinically indicated)																	
Serum pregnancy test (urine test allowed in safety FU)		S	S		S	S				S	S	S	S	S	S	S	S	S	S	
Thyroid Stimulating Hormone (TSH)		X	X		X	X				X	X	X	X	X						
Free T3 and Free T4		X	X (only if TSH is abnormal)																	
Hepatitis testing		X	X (if clinically indicated)																	
HIV History (HIV testing where locally required)		S																		
CT/MRI of chest, abdomen, and pelvis with i.v. contrast		X	X (every 8 weeks until PD determined by investigator and confirmed by BIRC per RECIST 1.1)																	
Brain CT/MRI with i.v.contrast		X	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)																	
CT/MRI of other metastatic sites (e.g., neck, etc.) if suspected		X	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)																	
Whole body bone scan		X	If clinically indicated																	
Localized CT, MRI, or X-Ray		X	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)																	
Color photographs (with metric ruler)		X	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)																	

Period	Screening		Treatment												Post treatment follow-up					
Visit Name	Molecular pre-screening	Main screening	C1		C2	C3				C4	C5	C6	Subsequent cycles	EOT	Safety Follow-up					Survival Follow-up
															30 day	60 day	90 day	120 day	150 day	
Days		-28 to -1	D1	D15	D1	D1	D4	D8	D15	D1	D1	D1	D1		-	-	-	-	-	every 12 weeks
Electrocardiogram (12-Lead ECG)		X	X		X	X								X						
[redacted]																				
Blood sample for Capmatinib **Extensive and non-Extensive** PK sampling						X				X										
Blood sample for Spartalizumab **Extensive** PK sampling			X			X	X	X	X	X		X	X (every 12 cycles from C18D1)	X (or at end of spartalizumab treatment)					X (if visit performed at site)	
Blood sample for Spartalizumab **non-Extensive** PK sampling			X			X				X		X	X (every 12 cycles from C18D1)	X (or at end of spartalizumab treatment)					X (if visit performed at site)	

Period	**Screening**		**Treatment**												**Post treatment follow-up**					
Visit Name	**Molecular pre-screening**	**Main screening**	**C1**		**C2**	**C3**				**C4**	**C5**	**C6**	**Subsequent cycles**	**EOT**	**Safety Follow-up**					**Survival Follow-up**
															30 day	**60 day**	**90 day**	**120 day**	**150 day**	
Days		**-28 to -1**	**D1**	**D15**	**D1**	**D1**	**D4**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**		**-**	**-**	**-**	**-**	**-**	**every 12 weeks**
[redacted]																				
IRT Registration/ Treatment Dispensing/ Discontinuation		X	X (study treatment dispensing only)											X						
Capmatinib administration			X (continuous BID dosing)																	
Spartalizumab administration			X		X	X				X	X	X	X							
Antineoplastic therapies since discontinuation of study treatment															X	X	X	X	X	X
Safety follow-up															X	X	X	X	X	
Survival status																				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.																				

Table 8-1b Assessment Schedule - Part 1 (Single Arm Run-in Part) – applicable upon approval of protocol amendment 01

Period	**Treatment**				**Post treatment follow-up***				
Visit Name	**C3**	**C4**	**Subsequent cycles**	**EOT**	**Safety Follow-up**				
					30 day	**60 day**	**90 day**	**120 day**	**150 day**
Days	**D1**	**D1**	**D1**		**-**	**-**	**-**	**-**	**-**
Concomitant medications	X (up to 150 days from last dose of spartalizumab or 30 days from last dose of capmatinib whichever is longer or start of new anti-neoplastic therapy).								
Adverse Events	X (up to 150 days from last dose of spartalizumab or 30 days from last dose of capmatinib whichever is longer, after start of new anti-neoplastic therapy only suspected AEs will be collected). For SAE reporting please refer to Section 10.								
Physical Examination	S	S	S	S					
Weight	X	X	X	X					
Vital signs	X	X	X	X					
Performance status	X	X	X	X					
Hematology	X	X	X	X					
Chemistry	X	X	X	X					
Urinanalysis	S (if clinically indicated)								
Coagulation	X (if clinically indicated)								
Serum pregnancy test (urine test allowed in safety FU)	S	S	S	S	S	S	S	S	S
Thyroid Stimulating Hormone (TSH)	At day 1 of every cycle up to 150 days after the last dose of spartalizumab, then as clinically indicated. or as clinically indicated in subjects who have never received spartalizumab treatment).								
Free T3 and Free T4	X (only if TSH is abnormal)								
Hepatitis testing	X (if clinically indicated)								
CT/MRI of chest, abdomen, and pelvis with i.v. contrast	X (every 8 weeks until at least 2 post-baseline assessment have been obtained then every 12 weeks thereafter								

Period	**Treatment**				**Post treatment follow-up***				
					Safety Follow-up				
Visit Name	**C3**	**C4**	**Subsequent cycles**	**EOT**	**30 day**	**60 day**	**90 day**	**120 day**	**150 day**
Days	**D1**	**D1**	**D1**		**-**	**-**	**-**	**-**	**-**
Brain CT/MRI with i.v.contrast	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated).								
CT/MRI of other metastatic sites (e.g., neck, etc.) if suspected	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)								
Whole body bone scan	If clinically indicated								
Localized CT, MRI, or X-Ray	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)								
Color photographs (with metric ruler)	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)								
Electrocardiogram (12-Lead ECG)	X			X					
Blood sample for Capmatinib **Extensive and non-Extensive** PK sampling	X	X							
IRT Registration/ Treatment Dispensing/ Discontinuation	X (study treatment dispensing only)				X				

Period	Treatment				Post treatment follow-up*				
					Safety Follow-up				
Visit Name	C3	C4	Subsequent cycles	EOT	30 day	60 day	90 day	120 day	150 day
Days	D1	D1	D1		-	-	-	-	-
Capmatinib administration	X (continuous BID dosing)								
Safety follow-up					X	X	X	X	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.

*Following the approval of protocol amendment 01, tumor assessment follow-up and survival follow-up will not be performed

Table 8-2 Assessment Schedule - Part 2 (Randomized part) - obsolete since Part 2 will not be initiated

Period	Screening		Treatment									Post treatment follow-up					
												Safety Follow-up					Survival Follow-up
Visit Name	Molecular pre-screening	Main screening	C1		C2	C3	C4	C5	C6	Subsequent cycles	EOT	30 day	60 day	90 day	120 day	150 day	
Days		-28 to -1	D1	D15	D1	D1	D1	D1	D1	D1		-	-	-	-	-	every 12 weeks
Informed consent for molecular pre-screening	X																
Confirmation of EGFR wt and ALK rearrangement negative status (local data)	X																
Collection of archival tumor sample or newly obtained tumor sample for central MET testing (if no local data available)	X																
Informed consent		X															
MET mutation status (result of central testing or local data, if available)	X																

Period	Screening		Treatment									Post treatment follow-up					
Visit Name	Molecular pre	Main screening	C1		C2	C3	C4	C5	C6	Subsequent cycles	EOT	Safety Follow-up					Survival Follow-up
												30 day	60 day	90 day	120 day	150 day	
Days		-28 to -1	D1	D15	D1	D1	D1	D1	D1	D1		-	-	-	-	-	every 12 weeks
[redacted]																	
Inclusion / Exclusion criteria		X															
Demography	X																
[redacted]																	
Smoking history		X															
Diagnosis and extent of cancer		X															
Prior antineoplastic therapy (meds, surgery, radiation)		X															
Relevant medical history/current medical conditions		X															
Concomitant medications		X (from screening until 150 day from last dose of spartalizumab/placebo or 30 days from last dose of capmatinib whichever is longer or start of new anti-neoplastic therapy)															
Adverse Events		X (from screening until 150 day from last dose of spartalizumab/placebo or 30 days from last dose of capmatinib whichever is longer, after start of new anti-neoplastic therapy only suspected AEs will be collected). For SAE reporting please refer to Section 10.															
Physical Examination		S	S	S	S	S	S	S	S	S	S						
Height		X															
Weight		X	X		X	X	X	X	X	X	X						
Vital signs		X	X	X	X	X	X	X	X	X	X						
Performance status		X	X		X	X	X	X	X	X	X						
Hematology		X	X	X	X	X	X	X	X	X	X						
Chemistry		X	X	X	X	X	X	X	X	X	X						

Period	Screening		Treatment								Post treatment follow-up					
Visit Name	Molecular pre	Main screening	C1		C2	C3	C4	C5	C6	Subsequent cycles	EOT	Safety Follow-up					Survival Follow-up
												30 day	60 day	90 day	120 day	150 day	
Days		-28 to -1	D1	D15	D1	D1	D1	D1	D1	D1		-	-	-	-	-	every 12 weeks
Urinalysis		S	S (if clinically indicated)														
Coagulation		X	X (if clinically indicated)														
Serum pregnancy test (urine test allowed in FU)		S	S		S	S	S	S	S	S	S	S	S	S	S	S	
Thyroid Stimulating Hormone (TSH)		X	X		X	X	X	X	X	X	X						
Free T3 and Free T4		X	X (only if TSH is abnormal)														
Hepatitis testing		X	X (if clinically indicated)														
HIV History (HIV testing where locally required)		S															
CT/MRI of chest, abdomen, and pelvis with i.v. contrast		X	X (every 8 weeks until PD determined by investigator and confirmed by BIRC per RECIST 1.1 (or until confirmed PD by Investigator [redacted] if subjects meets criteria for treatment beyond progression														
Brain CT/MRI with i.v.contrast		X	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)														
CT/MRI of other metastatic sites (e.g., neck, etc.) if suspected		X	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)														
Whole body bone scan		X	If clinically indicated														
Localized CT, MRI, or X-Ray		X	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)														
Color photographs (with metric ruler)		X	X (If positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.)														
Electrocardiogram (12-Lead ECG)		X	X		X	X					X						
[redacted]																	

Period	Screening		Treatment									Post treatment follow-up					
Visit Name	Molecular pre	Main screening	C1		C2	C3	C4	C5	C6	Subsequent cycles	EOT	Safety Follow-up					Survival Follow-up
												30 day	60 day	90 day	120 day	150 day	
Days		-28 to -1	D1	D15	D1	D1	D1	D1	D1	D1		-	-	-	-	-	every 12 weeks
[redacted]																	
Blood sample for Capmatinib **non-Extensive** PK sampling						X	X										
Blood sample for Spartalizumab/placebo **non-Extensive** PK sampling			X			X	X		X	X (every 12 cycles from C18D1)	X (or at end of spartalizumab treatment)					X (if visit performed at site)	
[redacted]																	
IRT Registration/ Randomization/ Treatment Dispensing/Discontinuation		X	X (study treatment dispensing only)								X						
Capmatinib administration			X (continuous BID dosing)														
Spartalizumab/placebo administration			X		X	X	X	X	X	X							
Antineoplastic therapies since discontinuation of study treatment												X	X	X	X	X	X
Safety follow-up												X	X	X	X	X	
Survival status																	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.																	

8.1 Screening

8.1.1 Molecular pre-screening

In order to be considered eligible for the study, subjects must have written documentation of EGFR wt and ALK rearrangements negative NSCLC (not required for subjects with pure squamous cell histology, for additional details see Section 5.1). The results from procedures performed as part of the local standard practices (prior to enrolling in the trial) will satisfy the inclusion criteria. The results of existing local METΔex14 mutation data (local assays must be approved by Novartis) must be captured on the appropriate eCRF upon enrollment onto the study after the subject has signed the main study ICF. Evidence of local data must be present in the source documentation at the site.

If METΔex14 mutation status is not known at the time of consideration for enrollment or the local assay data is not approved by Novartis, a tumor sample will be sent to a Novartis-designated central laboratory during the molecular pre-screening period to assess METΔex14 mutation (Molecular pre-screening requirements for tumor samples are detailed in Section 5.1).

All subjects requiring central MET testing will be asked to sign and date an IRB/IEC approved "Molecular pre-screening informed consent form" before their tumor sample is sent for testing to the Novartis-designated central laboratory.

The pre-screening results from central testing for all tested subjects (whether the subject is eligible or not for the study) will be communicated to the respective study center. If confirmed that the subject's tumor harbors the required mutation(s), the subject will be able to proceed for study specific screening procedures following signature of the main ICF.

Remaining tumor material from subjects that do not have METΔex14 mutation may be used for companion diagnostic development.

8.1.2 Main screening

The study IRB/IEC approved informed consent form must be signed and dated before any screening procedures are performed, except for laboratory and radiological evaluations which were performed as part of the 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 8-1 or Table 8-2). Screening assessments must be repeated if performed outside of the specified screening window (Section 8). Subjects must meet all inclusion and none of the exclusion criteria at screening in order to be eligible for the study.

In Part 2 of the study, PD-L1 status must be established prior to randomization to allow appropriate stratification of the subjects. If local PD-L1 expression data is available (Dako PD-L1 IHC 22C3 pharmDx assay results only), the results are requested to be entered into the eCRF pages and will be used for stratification purposes. If the status is unknown or it has been assessed with another assay, Dako PD-L1 IHC 22C3 pharmDx assay will be performed

at a local laboratory or at Novartis designated central laboratory and the result will be communicated to the site.

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 screening failure.

Re-screening of a subject who has failed screening may be allowed. In such cases, a new ICF must be signed. All required screening assessments must be repeated if they do not meet the allowed time window for screening when the subject is re-screened for participation in the study. An individual subject can only be re-screened once for the study.

8.1.3 Information to be collected on screening failures

Subjects who signed the molecular pre-screening ICF but are considered ineligible after molecular pre-screening, as well as subjects who are found ineligible after signing the main ICF will be considered as screening failures.

Subjects from Part 2 who are randomized and 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 Case Report Form.

The reason for molecular pre-screening failure or screening failure will be entered on the applicable disposition page on the eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screening failure subjects.

No other data will be entered into the clinical database for subjects who are screening failures, unless the subject experienced a Serious Adverse Event during the screening period (see Section 10). For molecular pre-screening failure subjects, only SAEs possibly related to a study procedure (i.e. tumor biopsy collection) will be reported to the Novartis safety group. For subjects who fail screening, SAEs will be reported in the database up to the screening failure date.

8.2 Subject demographics/other baseline characteristics

Data to be collected will include general subject demographics, smoking history, relevant medical history and current medical conditions, prior concomitant medications, diagnosis and extent of cancer, baseline tumor mutation status (MET, EGFR and ALK) and details of prior anti-neoplastic treatments.

Patient 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.

Additionally, the status of PD-L1, if already known and assessed by Dako PD-L1 IHC 22C3 pharmaDx, will be recorded on the eCRF. If this data is not available, central analysis of PD-L1 will be performed.

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

8.3 Efficacy

8.3.1 Tumor imaging

Following the approval of protocol amendment 01, the study imaging will no longer be collected and reviewed centrally. Centralized assessment of CNS lesions based on RANO BM criteria will not be performed.

Tumor response will be assessed locally according to the Novartis guideline version 3.2 (Appendix 1) based on RECIST 1.1 (Eisenhauer et al 2009) [redacted] (Seymour et al 2017) for subjects treated beyond initial disease progression as per RECIST 1.1.

The imaging assessment collection plan is presented in Table 8-3.

The central review of the scans will be carried out in a blinded fashion. Further details regarding the central review process will be described in the Blinded Independent Review Committee (BIRC) charter.

Table 8-3 Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI of chest, abdomen and pelvis with i.v. contrast	Mandated	Mandated every 8 weeks (+/- 7 days) until at least 2 post-baseline assessments have been obtained, then every 12 weeks thereafter until PD determined by investigator assessment (with or without confirmation by BIRC) or EOT. Following the approval of protocol amendment 01, tumor assessment follow up will not be performed and study imaging will no longer be reviewed by BIRC.
CT or MRI of brain with i.v. contrast	Mandated	Mandated if positive at baseline following the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.
CT or MRI of other metastatic sites (e.g., neck, etc.)	Mandated if metastatic sites are suspected	If other metastatic sites are positive at baseline, follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.
Whole body bone scan*	Mandated	If clinically indicated.
Localized bone CT, MRI or X-ray	Mandated for any lesions identified on the whole body bone scan that are not visible on the CT/MRI of chest, abdomen, and pelvis or brain	If positive at baseline follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.
Color photographs with a metric ruler	Mandated if skin metastases are present.	If positive at baseline follow the same schedule as CT/MRI of chest, abdomen, and pelvis. Or if clinically indicated.

*Whole body bone scan according to imaging vendor specifications.

8.3.1.1 Baseline imaging assessments

Imaging assessments should be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1) per Table 8-3. Any imaging assessments already completed during the regular work-up of the subject within 28 days prior to start of treatment (for Part 1) or prior to randomization (Part 2), including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after the first dose of treatment cannot be considered baseline images.

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 radiotherapy, it can be considered as a measurable lesion.

If a subject is known to have a contraindication to CT 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.

8.3.1.2 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 8-1b or Table 8-2). Imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) until at least 2 post-baseline imaging assessments have been acquired, then every 12 weeks thereafter until disease progression as determined by investigator assessment per RECIST 1.1 or until EOT, whichever occurs the earliest.

Note: Imaging assessments should be scheduled using the first dose of study treatment in Part 1 and the day of randomization for Part 2 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, by 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 disease progression per RECIST 1.1 (Appendix 1).

All complete responses (CRs) and partial responses (PRs) must be confirmed by a second assessment. If the second assessment is performed outside the normal window of scans, it should not be performed earlier than 4 weeks after the scan where the criteria for response were first met.

8.3.1.3 Confirmation of disease progression by BIRC

Following the approval of protocol amendment 01, current section will no longer be applicable.

Timepoints at which progression is determined locally

All subjects who have disease progression determined by the local investigator require an expedited central radiological review. Rapid image transmission to the imaging CRO should be accomplished by transferring the images electronically promptly after their acquisition. In all instances, the process at the imaging CRO will ensure that the central reviewers remain blinded to the results of the local assessment and the expedited nature of the review. The investigator seeking an expedited review must indicate this request to the imaging CRO on a designated form or by alternative means.

The imaging will undergo expedited central review (within 5 business days from the time of image receipt at the imaging CRO and once all applicable queries are resolved) and the results of the central review will be communicated to the site. While the investigator is awaiting the results of the central review, it is preferable that the subject continue on study treatment. However, during this time, the investigator should do whatever is medically necessary for his/her subject.

If the central review determines disease progression, then the subject will discontinue study treatment and subsequent tumor assessments are no longer required. Treatment beyond BIRC-confirmed progression can only be provided if the subject meets all requirements in Section 6.1.4.

If the central review does not determine disease progression, the subject should continue receiving the study treatment unless there is a medical need (i.e., rapid progression or clinical deterioration) for an immediate change in therapy.

Subjects will continue to have imaging performed as per protocol (Table 8-1 or Table 8-2, as applicable) until the central review determines disease progression.

Time points without locally determined progression

All imaging time points without locally determined progression must be submitted promptly to the imaging vendor designated by Novartis. Time points without locally determined progression will be read on a non-expedited basis as detailed in the BIRC charter. Results of these readings will not be communicated to the sites.

Treatment beyond disease progression

Following determination of disease progression, if the investigator believes the subject may derive benefit from continuing study treatment, the subject will be permitted to continue treatment beyond initial disease progression as per RECIST 1.1. Subjects enrolled in Part 2 will

be followed by the investigator [redacted]. Please see Section 6.1.4 for additional information.

Post-Treatment Efficacy Follow-up

Subjects who discontinue treatment for reasons other than disease progression as per RECIST 1.1 confirmed by BIRC will continue to perform tumor assessments every 8 weeks in parallel to the safety and/or survival follow-up until documented disease progression (see Section 9.2.2).

8.3.2 Overall survival

Following the approval of protocol amendment 01, current section is no longer applicable, as survival follow up will not be performed.

All subjects will enter the survival follow-up period after completion of the safety follow-up. Survival status will be collected every 12 weeks regardless of treatment discontinuation reason (except if consent is withdrawn or subject is lost to follow-up) until death, lost to follow-up, or withdrawal of consent for survival follow-up. Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

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

8.4 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 Section 10.

8.4.1 Physical examination

Physical examination will be performed according to Table 8-1b or Table 8-2, as applicable.

At screening and Cycle 1 Day 1 prior to treatment (Part 1) or prior randomization (Part 2), 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, vascular, and neurological systems.

From Cycle 1 Day 1 onwards, an abbreviated physical exam will be performed. It will include at least the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse).

More frequent examinations may be performed at the discretion of the investigator and if medically indicated. Information about the physical examination must be present in the source documentation.

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.

8.4.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.

Vital signs will be measured at screening and at subsequent time points as specified in Table 8-1b or Table 8-2, as applicable.

8.4.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-1b or Table 8-2, as applicable.

8.4.4 Performance status

The Eastern Cooperative Oncology Group (ECOG) Performance Status Scale will be used as described in Table 8-4, following the schedule given in Table 8-1b or Table 8-2, as applicable.

Table 8-4 ECOG Performance Status

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

8.4.5 Laboratory evaluations

The laboratory tests that will be assessed as part of the safety monitoring are listed in Table 8-5. For subjects enrolled in Part 1, all parameters will be analyzed locally. For subjects enrolled in Part 2, hematology, clinical chemistry, coagulation and thyroid parameters will be assessed at a Novartis-designated central laboratory and all other tests will be performed locally.

The frequency of these assessments is indicated in Table 8-1b or Table 8-2, as applicable. 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.

The site does not need to wait for the results of centrally-analyzed laboratory assessments when an immediate clinical decision needs to be made (e.g. confirmation of eligibility, study drug interruption, re-initiation, and/or termination) and in those cases locally unscheduled testing may be performed and used for eligibility assessments. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators separately in the central laboratory manual.

The results of the laboratory tests performed locally will be recorded in the eCRF, unless differently specified in Table 8-1b or Table 8-2. Novartis must be provided with a copy of the normal ranges and certification of the all laboratories used to assess subjects' safety during study conduct, when possible. The investigator is responsible for reviewing all laboratory reports for subjects in the study and evaluating any abnormalities for clinical significance.

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

Table 8-5 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells, , Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other (absolute value preferred , %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Total Bilirubin, Direct/Indirect Bilirubin (only if total bilirubin is ≥ grade 2), Blood Urea Nitrogen (BUN) or Urea, Amylase, Lipase, fasting Glucose (non-fasting glucose allowed post-baseline). Bicarbonate, Chloride and Uric Acid: at screening and thereafter as clinically indicated.
Urinalysis	Local Laboratory: Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If dipstick is abnormal then perform local laboratory Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Thyroid	TSH (Thyroid Stimulation Hormone), Free T3 and Free T4
Hepatitis markers	HBV-DNA*, HBsAg, HBsAb, HBcAb (IgG), HCV Ab, HCV RNA-PCR*
Pregnancy Test	A serum pregnancy test must be performed at screening within ≤ 72 hours before first dose of study treatment, then the schedule of serum pregnancy tests should be performed monthly as indicated in Table 8-1b and Table 8-2. During the safety follow-up period, urine pregnancy test can be performed instead of serum pregnancy test. If local requirements dictate otherwise, local regulations should be followed.

* HBV DNA test not required if HBsAg, HBsAb and HBcAb are all negative; HCV RNA test not required if HCV Ab is negative.

8.4.5.1 Hematology

Hematology tests are to be performed according to the visit schedule outlined in Table 8-1b or Table 8-2, as applicable. For details of the hematology panel refer to Table 8-5. Hematology should be assessed on the actual scheduled day, even if study drug is being withheld.

Hematology lab tests done as part of screening assessments ≤ 72 hours (3 days) of first dose of study treatment do not need to be repeated.

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

8.4.5.2 Clinical chemistry

Clinical chemistry tests are to be performed according to the visit schedule outlined in Table 8-1b or Table 8-2, as applicable. For details of the biochemistry panel see Table 8-5. Biochemistry should be assessed on the actual scheduled day, even if study drug is being withheld.

Chemistry lab tests done as part of screening assessments ≤ 72 hours (3 days) prior to the first dose of study treatment do not need to be repeated.

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

8.4.5.3 Urinalysis

Urinalysis Dipstick measurements will be performed as per Table 8-5 and according to the schedule of assessments (Table 8-1b or Table 8-2, as applicable). Any significant findings on dipstick will be followed up with microscopic evaluation.

8.4.5.4 Coagulation

Coagulation tests outlined in Table 8-5 will be performed according to the visit schedule outlined in Table 8-1b or Table 8-2, as applicable.

8.4.5.5 Thyroid function

Thyroid function (TSH and Free T3 and T4) will be tested as outlined in Table 8-1b or Table 8-2. After screening, Free T3 and T4 will only be tested if TSH is abnormal.

8.4.5.6 Hepatitis marker

Hepatitis panels outlined in Table 8-5 will be performed at screening and as clinically indicated while on study treatment and until 30-day safety follow-up (for example to rule out viral causality in case of suspected DILI).

HBV and HCV testing will be performed at screening (≤ 28 days prior to start of study treatment) and as clinically indicated (hepatitis markers should be evaluated for precautionary safety monitoring of viral re-activation while on study treatment).

During the screening period, subjects must be screened for HBV and HCV (current or past history of infection). Careful medical history must be taken for all subjects to look for risk factors (family history of HBV and HCV, intravenous drug abuse, unprotected sex, dialysis, blood transfusions, etc.), and any past or present HBV symptoms (e.g., jaundice, dark urine, light colored stools, right upper quadrant pain).

Hepatitis B:

At screening, all subjects will be tested for:

- HBV-DNA level (test not required if HBsAg, HBsAb and HBcAb are all negative.)
- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core antibody (HBcAb IgG)
- Hepatitis B surface antibody (HBsAb)

Hepatitis C:

At screening, all subjects will be tested for HCV Ab and HCV RNA-PCR. If the HCV Ab test is negative, HCV RNA test is not required.

8.4.6 Electrocardiogram (ECG)

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

Standard triplicate 12 lead ECG recording will be performed at the time points indicated in Table 8-6. The individual ECGs should be recorded approximately 2 minutes apart.

The Fridericia QT correction formula (QTcF) should be used for clinical decisions. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each subject.

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 baseline before administration of study treatment.

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

ECGs are to be collected with machines available at the site. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate eCRF. Each ECG tracing should be labeled with the study number, 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 adverse events.

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

Table 8-6 Local ECG collection plan

Cycle	Day	Time	ECG Type
Screening		Anytime	12 Lead, triplicate
1	1	Pre-dose	12 Lead, triplicate
2	1	Pre-dose	12 Lead, triplicate
3	1	Pre-dose	12 Lead, triplicate
End of treatment		Anytime	12 Lead, triplicate
Unscheduled ECG		Anytime if clinically indicated	12 Lead, triplicate

8.4.7 Pregnancy and assessments of fertility

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

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. During the study, serum pregnancy testing should be done at screening and/or within 72 hours prior to the first dose of study treatment and then at monthly intervals until the end of the safety follow-up period.

In case the subject is not coming to the clinic during the safety follow-up period, urinary pregnancy tests can be performed monthly at home or at a local doctor's office until 150-day after the last dose of spartalizumab/placebo or 30 days after last dose of capmatinib, whichever is longer. The results will be communicated to the site staff. These follow-up pregnancy tests will be recorded only in the source documentation, not on the eCRF. In case of a positive urine pregnancy result, **the subject must contact** the investigator immediately and the study treatment must be stopped until additional tests are performed to confirm pregnancy (including a confirmatory serum pregnancy test).

The subject must discontinue his study treatment in case of confirmed pregnancy and the site should follow the reporting requirements as described in Section 10.1.4.

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.

8.4.8 Appropriateness of safety measurements

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

8.5 Additional assessments

[redacted]

[redacted]

8.5.2 Pharmacokinetics

Blood samples will be collected from all subjects for the analysis of plasma capmatinib and serum spartalizumab concentrations, [redacted].

8.5.2.1 Pharmacokinetic blood collection and handling

The exact date and clock times of drug administration and PK blood draw will be recorded on the appropriate eCRF 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 2 mL of blood will be collected for spartalizumab analysis in serum [redacted] For time points when spartalizumab PK [redacted] are to be measured, a single blood sample will be collected for [redacted] spartalizumab PK. **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 [redacted] samples.

If subjects experience a SAE or an 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.

8.5.2.2 Pharmacokinetic sampling for capmatinib

PK blood samples for capmatinib will be collected for all the subjects as outlined in Table 8-7 and Table 8-8. Extensive PK samples will be collected on cycle 3 day 1 from the first fifteen subjects enrolled in Part 1.

Table 8-7 Capmatinib pharmacokinetic blood collection log for extensive PK collection (first 15 subjects of Part 1)

Cycle	Day	Scheduled Time (h)
3	1	Pre-dose[1]
3	1	1h (±10min)
3	1	2h (±15min)
3	1	4h (±30min)

Cycle	Day	Scheduled Time (h)
3	1	8h (±120 min)
4	1	Pre-dose[1]
4	1	Anytime within 1-4h
Unscheduled		anytime

[1] Take samples immediately prior to administration of capmatinib.

Table 8-8 Capmatinib pharmacokinetic blood collection log for non-extensive PK collection (remaining subjects of Part 1 and all Part 2 subjects)

Cycle	Day	Scheduled Time (h)
3	1	Pre-dose[1]
3	1	Anytime within 1-4h
4	1	Pre-dose[1]
4	1	Anytime within 1-4h
Unscheduled		anytime

[1] Take samples immediately prior to administration of capmatinib.

8.5.2.3 Pharmacokinetic [redacted] sampling for spartalizumab

Following the approval of protocol amendment 01, PK [redacted] sampling for spartalizumab will not be performed, except in the event of a clinically significant AE or if [redacted] is suspected up to 150 days from last dose of spartalizumab.

Blood samples for spartalizumab PK [redacted] analysis will be collected for all the subjects as outlined in Table 8-9 and Table 8-10. PK [redacted] samples will be collected at the time of study treatment discontinuation (EOT visit) or when spartalizumab treatment is discontinued (in case spartalizumab is prematurely discontinued due to toxicity). The 150-days safety follow-up sample will only be collected if the visit is performed at site. Extensive PK samples will be collected in cycle 3 from the first fifteen subjects enrolled in Part 1. PK [redacted] samples will be collected also in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if [redacted] is suspected. No additional PK [redacted] samples will be collected after the cut-off of the primary CSR.

Table 8-9 Spartalizumab pharmacokinetic [redacted] blood collection log for extensive PK sample collection (first 15 subjects of Part 1) - obsolete upon approval of protocol amendment 01

Cycle	Day	Scheduled Time (h)	Analytes
1	1	Pre-dose[1]	PK[redacted]
3	1	Pre-dose[1]	PK[redacted]
3	1	1h (±5min)	PK
3	4	72h (±8h)	PK
3	8	168h (±8h)	PK
3	15	336h (±24h)	PK
4	1	Pre-dose[1]	PK[redacted]
6	1	Pre-dose[1]	PK[redacted]

Cycle	Day	Scheduled Time (h)	Analytes
Every 12 cycles after C6D1 until discontinuation of spartalizumab treatment	1	Pre-dose[1]	PK/[redacted]
EOT[2]		anytime	PK/[redacted]
150-day safety follow-up[3]		anytime	PK/[redacted]
Unscheduled		anytime	

[1] Take samples immediately prior to infusion of spartalizumab
[2] Samples to be collected at the time of study treatment discontinuation (EOT visit) or when spartalizumab treatment is discontinued
[3]Only applicable for subjects who return to the site for 150-day safety FU visit

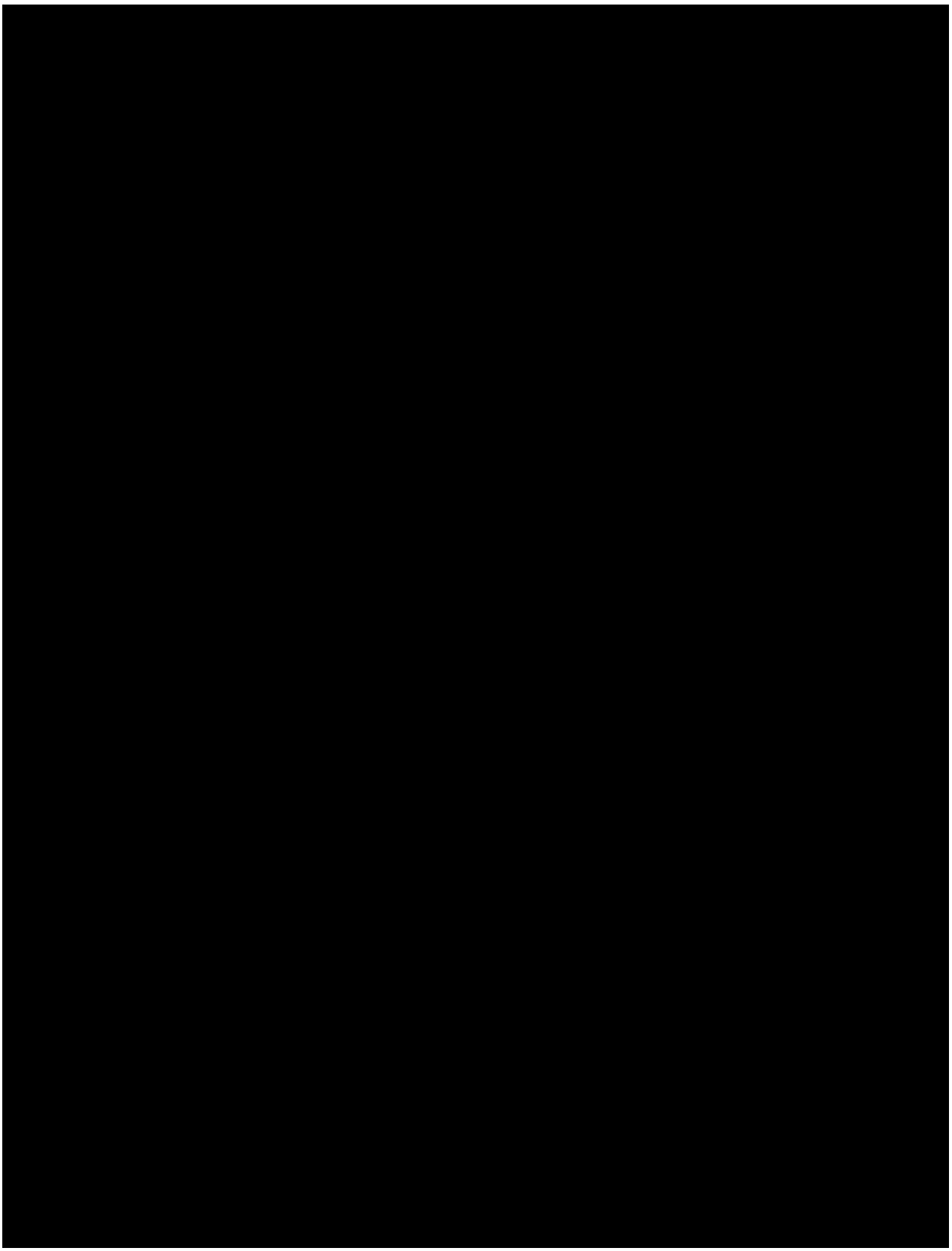
Table 8-10 Spartalizumab/placebo pharmacokinetic [redacted] blood collection log for non-extensive PK collection (remaining subjects of Part 1 and all Part 2 subjects) - obsolete upon approval of protocol amendment 01

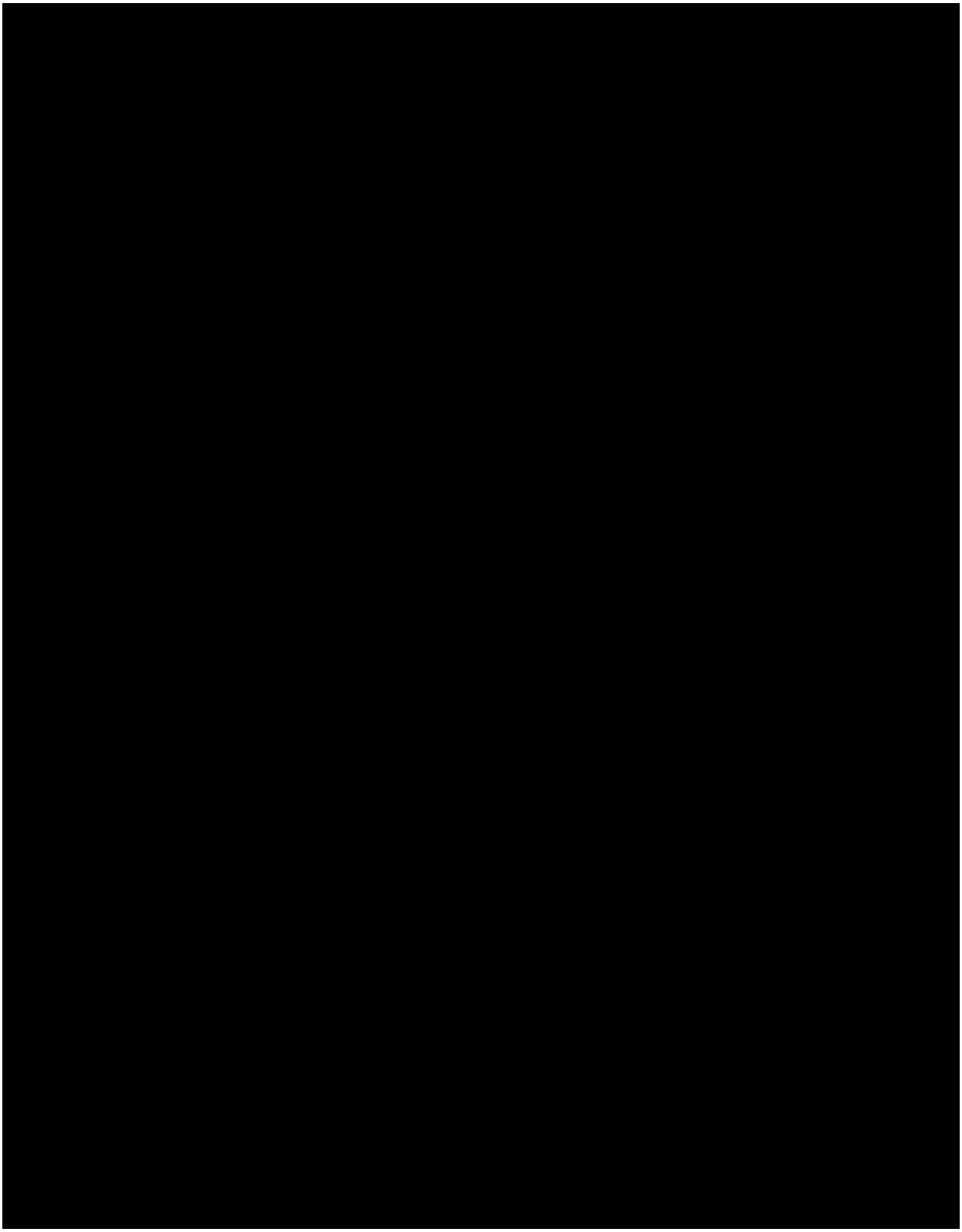
Cycle	Day	Scheduled Time (h)	Analytes
1	1	Pre-dose[1]	PK[redacted]
3	1	Pre-dose[1]	PK[redacted]
4	1	Pre-dose[1]	PK[redacted]
6	1	Pre-dose[1]	PK[redacted]
Every 12 cycles after C6D1 until discontinuation of spartalizumab/placebo treatment	1	Pre-dose[1]	PK[redacted]
EOT[2]		anytime	PK[redacted]
150-day safety follow-up[3]		anytime	PK[redacted]
Unscheduled		anytime	

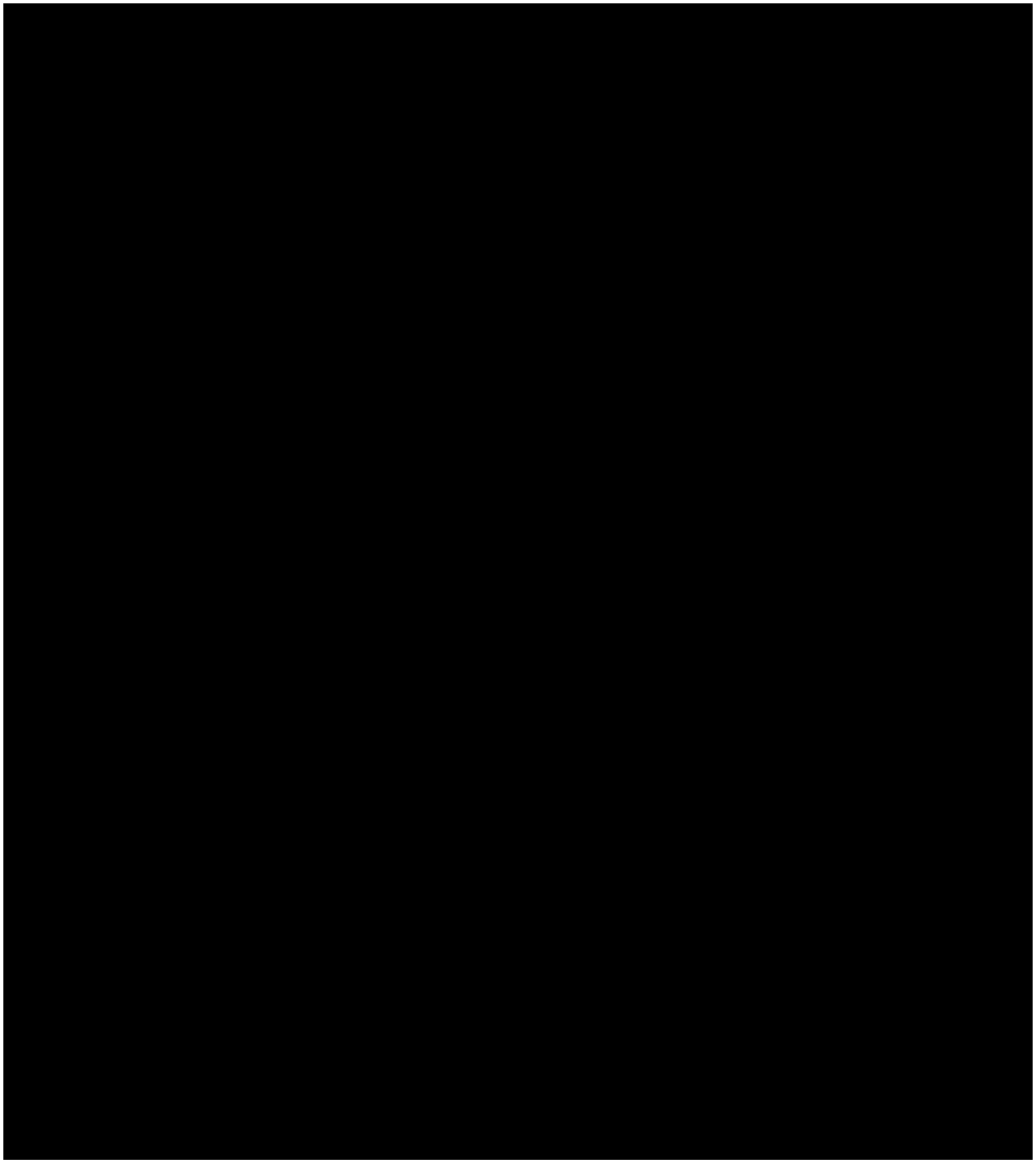
[1] Take samples immediately prior to infusion of spartalizumab/placebo
[2] Samples to be collected at the time of study treatment discontinuation (EOT visit) or when spartalizumab/placebo treatment is discontinued
[3] Only applicable for subjects who return to the site for 150-day safety FU visits

8.5.2.4 Analytical method

Pharmacokinetic samples for spartalizumab and capmatinib will be quantified using validated liquid chromatography tandem-mass spectrometry (LC/MS/MS) assays. The assay to quantify and assess the [redacted] will be a validated homogeneous ELISA.







9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped, and 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. An end of treatment visit will be performed when subjects permanently discontinue the study treatment to which they were assigned at study entry.

Study treatment must be discontinued under the following circumstances:

- Disease progression per RECIST 1.1 as determined by investigator assessment (with or without confirmation by BIRC). In some circumstances subjects may be allowed to continue to receive study treatment beyond disease progression as per RECIST 1.1. These subjects will continue assessments as outlined in Table 8-1b and will complete the EOT visit only after permanent discontinuation of study treatment (see Section 6.1.4)
- Subject/guardian decision
- Investigator decision
- Any situation in which study participation might result in a safety risk to the subject.
- Protocol deviation that results in a significant safety risk to the subject
- Adverse event requiring permanent discontinuation of study treatment (see Table 6-3)
- Pregnancy
- Death

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 Section 9.1.2). **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 Section 9.1.3. 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.

9.1.1.1 Replacement policy

Subjects will not be replaced on study. All treated subjects will contribute to the final analyses.

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 only 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 Table 8-1b or Table 8-2, as applicable.

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 or until the end of the study.

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 due to safety reasons, subjects must be seen as soon as possible 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 Novartis 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

Study completion is defined as when the end of study criteria are met or, in the event of an early study termination decision, the date of that decision.

9.2.1 End of Study

The end of study for Part 1 is defined as the earliest occurrence of one of the following:

- All subjects have discontinued study treatment and completed the safety follow-up, or have died, withdrawn consent or are lost to follow-up.
- Another clinical study or an alternative treatment option becomes available to continue the provision of campmatinib, and all subjects ongoing are transferred to that clinical study or alternative treatment option. For subjects who had received at least one dose of spartalizumab, all required safety assessments up to 150 days from the last dose of spartalizumab treatment must be completed and at least 2 post-baseline tumor assessments are obtained for the purpose of primary outcome measure completion before a transfer to another clinical study or alternative treatment option to continue capmatinib treatment may be initiated. Note: For subjects who transfer to another clinical study or an alternative treatment option to continue provision of study treatment, the follow-up for safety, tumor assessment and survival will not be performed.

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

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

9.2.2 Post treatment follow-up

After treatment discontinuation, all subjects will be followed for safety, as described in Section 9.2.2.1.

Note: For subjects who transfer to another clinical study or an alternative treatment option to continue provision of study treatment, the follow-up for safety, tumor assessment and survival will not be performed.

9.2.2.1 Safety follow-up

All subjects must have safety evaluations for 150 days after the last dose of spartalizumab/placebo and 30 days after the last dose of capmatinib, whichever is longer. The subject will be followed via telephone call or onsite visit (if patient happens to be visiting the site) for the 30-, 60-, 90-, 120- and 150-day follow-up visits. Concomitant medications will be collected until the 30-day safety follow-up has been completed or the start of a new anti-neoplastic therapy, whichever occurs first.

For female subjects of child bearing potential, pregnancy tests will be performed as outlined in Section 8.4.7.

The assessments required during safety follow-up are specified in Table 8-1b or Table 8-2.

9.2.2.2 Survival follow up

Following the approval of protocol amendment 01, survival follow up will not be performed.

After completion of the safety follow-up, subjects will enter the survival follow-up period. Subjects will be contacted by telephone every 12 weeks to follow-up on their survival status. Any new anti-neoplastic therapies that have been started since the last contact date will also be collected during these phone calls. Date of progression on new antineoplastic therapies will also be collected.

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.

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

Subjects whose MET mutation status is known will sign the main study ICF. AE collection starts at time of main study informed consent whether the subject is a screen failure or not.

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. CTCAE (version 5.0) grade. Grade 1 to 5 will be used to characterize the severity of the events.
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 a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn
6. its outcome

If the event worsens the event should be reported a second time on the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported on 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 after the last dose of capmatinib or 150 days after the last dose of spartalizumab/placebo, whichever is longer. If a patient starts a post treatment anti-neoplastic therapy sooner than the 30/150 days mentioned above, then only adverse events suspected to be related to study treatment should be collected.

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (i.e. as per RECIST 1.1), should not 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 and spartalizumab Investigator's Brochure.

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

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

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:

1. fatal
2. life-threatening. Life-threatening in the context of a 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).
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly/birth defect
5. 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 a SAE given above and not resulting in hospital admission

6. 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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors) should not be reported as a serious adverse event. However, progressive disease should be reported as an SAE if the investigator considers that the progression is related to the study treatment (e.g. disease progression greater/faster than what would be normally expected for the patients in this setting).

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 the end of the safety follow-up period (i.e. 30 days after the last dose of capmatinib or 150 days following the last dose of spartalizumab/placebo, whichever is longer), must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail).. If during the safety follow-up period, a subject starts a post-treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment will be collected.

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

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

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

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

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

For subjects with known MET mutation status who sign the main study ICF, SAE collection starts at time of main study informed consent whether the subject is a screen failure or not.

10.1.4 Pregnancy reporting

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

Pregnancy outcomes should be collected for the female partners of any male who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother. In addition, the newborn will be followed for up to 12 months after birth.

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

10.2 Additional Safety Monitoring

10.2.1 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

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

Adverse events of special interest to be monitored for capmatinib include:

- Hepatotoxicity,
- Nausea/Vomiting,
- Peripheral oedema,
- Renal dysfunction,
- ILD/pneumonitis,
- Central nervous system toxicity,

- Increased amylase/lipase,
- Phototoxicity,
- Teratogenicity

Adverse events of special interest to be monitored for spartalizumab include:

- Endocrinopathies (i.e. hypothyroidism, hyperthyroidism, diabetes, hypophysitis, hypopituitarism, adrenal insufficiency)
- Pneumonitis
- Colitis
- Hepatitis
- Nephritis
- Skin reactions
- Other immune-mediated events
- Infusion reactions

10.2.2 Data Monitoring Committee

Following the study enrollment halt during Part 1, Part 2 will not be initiated. This section is no longer applicable.

This study will institute 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 constituted after the decision to initiate Part 2 is taken and prior to the randomization of the first subject in Part 2.

The DMC will be responsible for reviewing the efficacy results from efficacy interim for PFS and the interim analysis for OS, as well as overseeing the safety data accruing in the trial at defined intervals. Also, if requested by the DMC Chair, additional safety reviews may be performed.

DMC will recommend to the sponsor whether to continue, modify or terminate the trial.

An independent statistical group external to Novartis, not involved in the trial conduct, will prepare data reports for the DMC. Details will be presented 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.

10.2.3 Steering Committee

A steering committee (SC) will be established comprising investigators participating in the trial, i.e. not members of the DMC, and Novartis representatives from the clinical trial team. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also

develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in a SC charter.

11 Data collection and database management

11.1 Data collection

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

The investigator/designee is responsible for assuring that the data (recorded on eCRFs) (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 adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **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's meeting, a Novartis or a designated Clinical Research Organization (CRO) representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA or a designated CRO. 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 demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs 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 eCRFs 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

Following the study enrollment halt during Part 1, Part 2 will not be initiated. Therefore, analysis and statistical methods for Part 2 are not applicable.

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

Study data in Part 1 will be reported in the final clinical study report (CSR) based on all subjects' data up to the time of completion of the study. There will be no additional CSR.

All summaries, listings, figures and analyses will be performed for all subjects.

Screen failure subjects, as described in Section 8.1.3, and the reasons for not starting the study treatment (for Part 1) or for not being randomized (for Part 2) 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

Part 1: Single Arm Run-in Part

Full Analysis Set (FAS)

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned and who received at least one dose of study treatment (i.e. at least one dose of any component of the study treatment that is capmatinib or spartalizumab (including incomplete infusion)).

Safety Set (SS)

See definition of the FAS.

Pharmacokinetic Analysis Set (PAS)

The capmatinib PAS includes two sets in Part 1, the capmatinib full pharmacokinetic analysis set (INC-FPAS) which will be used for NCA analysis and capmatinib pharmacokinetic analysis set (INC-PAS).

The INC-FPAS includes all subjects who have provided an evaluable PK profile (only applicable to subjects with extensive PK sampling). A profile is considered evaluable if all of the following conditions are satisfied:

- Subject has received one dose of the planned capmatinib treatment
- Subject has provided at least one valid primary PK parameter
- Subjects did not vomit within 4 hours after the dosing of capmatinib

The INC-PAS includes all subjects who have provided at least one evaluable PK concentration. For a concentration to be evaluable, a subject must:

- Have taken a dose of capmatinib prior to sampling
- For pre-dose samples, do not vomit within 4 hours after the dosing of capmatinib prior to sampling.
- For post-dose samples, do not 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 spartalizumab PAS includes two sets in Part 1, spartalizumab full pharmacokinetic analysis set (PDR-FPAS) and spartalizumab pharmacokinetic analysis set (PDR-PAS).

The PDR-FPAS includes all subjects who provide an evaluable PK profile (Note: Only applicable to subjects with extensive PK sampling). A profile is considered evaluable if all of the following conditions are satisfy:

- Subject has received one dose (complete infusion) of the planned spartalizumab treatment
- Subject has provided at least one valid primary PK parameter
- For pre-dose samples, have the sample collected before the next dose administration.

The PDR-PAS includes all subjects who have provided at least one evaluable PK concentration. For a concentration to be evaluable, a subject must:

- Have received one of the planned doses (complete infusion) of spartalizumab prior to sampling.
- For pre-dose samples, have the sample collected before the next dose administration.

[redacted]

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated.

Full Analysis Set (FAS)

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

Safety Set (SS)

The Safety Set (SS) comprises all subjects who received at least one dose of the study treatment (i.e. at least one dose of any component of the study treatment that is capmatinib or spartalizumab/placebo (including incomplete infusion)). Subject will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

Pharmacokinetic Analysis Set (PAS) [redacted]

The INC-PAS, PDR-PAS [redacted] set will be defined in Part 2 and will share the same definition of Part 1.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for the FAS by study part (overall for Part 1; and by treatment group and overall for Part 2).

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, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized and listed for the FAS by study part.

12.3 Treatments

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

The duration of exposure to study treatment 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 for each study drug (capmatinib or spartalizumab/placebo) and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized and listed.

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

12.4.1 Efficacy endpoint(s) / estimand(s)

Part 1: Single Arm Run-in Part

The primary objective is to evaluate the anti-tumor activity of capmatinib in combination with spartalizumab, as measured by overall response rate (ORR) by investigator assessment according to RECIST 1.1 (see Appendix 1). The analysis will be performed on the FAS.

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated.

The primary objective is to evaluate whether spartalizumab in addition to capmatinib prolongs progression free survival (PFS) by BIRC according to RECIST 1.1 (see Appendix 1) compared to capmatinib plus placebo. The analysis will be performed on the FAS.

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

Overall response rate (ORR)

ORR is defined as the proportion of subjects with a confirmed best overall response (BOR) of complete response (CR) and partial response (PR) as per investigator assessment according to RECIST 1.1 (see Appendix 1).

Progression free survival (PFS)

PFS is defined as the time from the date of randomization to the date of the first documented progression according to RECIST 1.1, or death due to any cause. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. PFS will be assessed by BIRC according to RECIST 1.1. Censoring conventions (i.e. handling of missing values/censoring/discontinuations) are provided in Section 12.4.1.4.

12.4.1.2 Statistical hypothesis, model, and method of analysis

Part 1: Single Arm Run-in Part

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

Participants who had never received one of the investigational drugs will be excluded from the efficacy analysis.

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated.

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

$$H_{01}: \theta_1 \geq 1 \text{ vs } H_{11}: \theta_1 < 1$$

Where θ_1 is the PFS hazard ratio (HR) (capmatinib in combination with spartalizumab versus capmatinib plus placebo). The stratification will be based on the stratification factors assigned at randomization (i.e. presence or absence of brain metastasis at baseline [as assessed investigator per RECIST 1.1] and PD-L1 expression [<1%, or 1-49%, or ≥50%]).

The PFS will be analyzed at the interim analysis and final analysis of a group sequential design, using a Lan-DeMets (O'Brien and Fleming 1979) alpha spending function.

PFS will be summarized using the Kaplan-Meier (KM) method, based on FAS. Median PFS, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented by treatment group. KM estimates for PFS proportions at specific timepoints, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided. The hazard ratio for PFS will be estimated, along with its 95% confidence interval, using a stratified Cox proportional hazard model using the same stratification factors as for the log-rank test. If there are too few patients/events in a given stratum, strata might be grouped for the analysis. Further details will be provided in the SAP.

If PFS is not statistically significant at the PFS interim analysis:

PFS data will be tested at the time of the final PFS analysis.

If PFS is statistically significant at the PFS interim analysis:

The subsequent PFS analysis will still be performed to obtain more PFS data and additional follow-up PFS analyses may also be performed earlier than planned primary PFS analysis at the request of Health Authorities or to facilitate health authority interactions. Note that in this case, the PFS analysis will only be descriptive and no statistical testing will be performed for the analysis.

12.4.1.3 Handling of intercurrent events of primary estimand

Part 1: Single Arm run-in Part

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

- **Discontinuation of spartalizumabfor any reason:** BOR will take into account all available tumor assessments irrespective of spartalizumab discontinuation reasons.
- **Discontinuation of tumor assessment follow up with approval of protocol amendment:** BOR will take into account all available tumor assessments up to the last valid tumor assessment prior to approval of protocol amendment.
- **Any public health emergency as declared by local or regional authorities, e.g., pandemic, epidemic or natural disaster:** BOR will take into account all tumor assessments irrespective of any public health emergency.
- **New anti-neoplastic therapy:** Tumor assessment data collected after starting new anti-neoplastic therapy will be excluded from the BOR derivation.

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated.

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

- **Discontinuation of study treatment for any reason before radiological progression or death due to any cause:** tumor assessment data collected after discontinuation of study treatment (or spartalizumab only) will be used for PFS
- **New anti-cancer therapy before radiological progression or death due to any cause:** PFS events documented after the start of new anti-cancer therapy will be used to derive the time to event for the primary analysis

- **Radiological progression or death observed after 2 or more missing tumor assessments:** radiological progression or death observed after 2 or more missing tumor assessments will not be included in the derivation of the time to event for PFS, and the observation will be censored at the time of the last adequate tumor assessment prior to the first missing assessment
- **Lack of post-baseline tumor assessment:** Subjects without a post-baseline tumor assessment will be censored at the time of the randomization

12.4.1.4 Handling of missing values/censoring/discontinuations

Part 1: Single Arm Run-in Part

Subjects in the FAS with unknown best overall response (BOR) will be noted as such in the appropriate tables/listings and counted as non-responders in the ORR calculation.

If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression or death is reported.

If any new anti-neoplastic therapy is taken while on study any subsequent assessments would be excluded from the BOR derivation.

Subjects without confirmed CR/PR, due to lack of subsequent tumor assessment after one CR/PR, will be considered as non-responders.

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated.

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

12.4.1.5 Sensitivity and supplementary analyses

Part 1: Single Arm Run-in Part

A sensitivity analysis may be performed where subjects without a valid post-baseline assessment (unless PD or death is reported before that time) are excluded from the calculation of the ORR.

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated.

Sensitivity Analyses

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

Supplementary Analyses

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

1. an unstratified and covariate unadjusted Cox model.
2. a stratified and covariate adjusted Cox model including as covariates the following: gender, age groups (<65, ≥65 years), ECOG PS (0, 1), histology (squamous, non-squamous), smoking status (smoker, non-smokers, ex-smokers), race (Asian, other). A list of covariates will be defined in the SAP.
3. If the primary analysis of PFS is statistically significant, sub group analysis to assess the homogeneity of the treatment effect across demographics and baseline characteristics will be performed. The following subgroups may be considered: gender, age groups (<65, ≥65 years), ECOG PS (0, 1), histology (squamous, non-squamous), smoking status (smoker, non-smokers, ex-smokers), race (Asian, other), presence or absence of brain metastasis at baseline (as assessed investigator per RECIST 1.1) and PD-L1 expression (<1%, or 1-49%, or ≥50%). A final list of subgroups of interest will be defined in the SAP.

Additional key supplementary analysis will be performed to take into account the possible delayed immunotherapy response (e.g. weighted log-rank test with Fleming-Harrington class of weights) and to assess the robustness of the primary analysis results for PFS. A weighted log-rank test using Fleming-Harrington class of weights will be used. Such analyses will be detailed in the SAP.

If proportional hazard assumption is violated as a result of a delayed treatment effect, a stratified piecewise Cox regression analysis will be performed based on PFS to estimate a hazard ratio within pre-specified time periods (0-3 months and >3 months, based on an assumed 3 months delay effect for PFS). The analysis will be performed by incorporating a time-dependent covariate into the model and estimating the treatment effect for each of the two time periods. The hazard ratio, 95% CIs and Wald P-value will be provided for each time period.

12.5 Analysis of secondary endpoints / estimands

12.5.1 Key secondary endpoint (Part 2: Randomized Part)

Following the study enrollment halt during Part 1, Part 2 will not be initiated. Therefore, analysis and statistical methods for Part 2 are not applicable.

The key secondary objective is to evaluate whether spartalizumab when added to capmatinib prolongs OS compared to capmatinib plus placebo. The analysis will be performed on the FAS.

OS is defined as the time from the date of randomization to the date of death due to any cause. If the subject is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cut-off date.

The following null and alternative hypothesis will be tested to address the key secondary objective for OS:

$$H_{02}:\theta_2 \geq 1 \text{ vs } H_{12}: \theta_2 < 1$$

Where θ_2 is the OS hazard ratio (capmatinib in combination with spartalizumab versus capmatinib plus placebo). The key secondary analysis to test these hypotheses and compare the two treatment groups will consist of the stratified log-rank test at an overall one-sided 2.5% significance level. The stratification will be based on the stratification factors assigned at randomization (i.e. presence or absence of brain metastasis (as assessed by investigator per RECIST 1.1) and PD-L1 expression [<1%, or 1-49%, or ≥50%]).

A maximum of four analyses are planned for OS. OS will be hierarchically tested in the following way:

1. at the time of the interim analysis for PFS when approximately 49% (96 deaths) are expected to occur. If PFS is statistically significant at this stage, OS will also be tested. If PFS is not statistically significant at this stage, then OS will not be tested. Note that if OS is not tested a conservative approach is used where some alpha, corresponding to the information fraction of OS events available at that time, will be spent.
2. at the time of the final analysis for PFS when approximately 75% (146 deaths) are expected to occur. If PFS is statistically significant at this stage, OS will also be tested. If PFS is not statistically significant at this stage, then OS will not be tested.
3. When approximately 85% of the deaths have been observed (167 deaths) in case the time gap between the final analyses for PFS and for OS is longer than 1 year. If PFS is not statistically significant, at the interim or the primary analysis, OS will not be tested.
4. at the final OS analysis of a group sequential design. If PFS is not statistically significant, at the interim or the primary analysis, OS will not be tested.

The type I error will be controlled using a Lan-DeMets (O'Brien and Fleming 1979) alpha spending function for OS which is independent of the one used for PFS. This guarantees the protection of the overall type I error ($\alpha = 2.5\%$) across all hypotheses and the repeated testing of the OS hypotheses at the interim and the final analyses (Glimm et al 2010).

OS will be summarized using the KM method, based on FAS. Median OS, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented by treatment group. KM estimates for OS proportions at specific timepoints, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided. The hazard ratio for OS will be estimated, along with its 95% confidence interval, using a stratified Cox proportional hazard model using the same stratification factors as for the log-rank test. If there are too few patients/events in a given stratum, strata might be grouped for the analysis. Further details will be provided in the SAP.

12.5.1.1 Handling of intercurrent events of key secondary estimand

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

- **Discontinuation of study for any reason:** OS will be analyzed based on the survival follow-up irrespective of the study discontinuation. OS will be censored at the last contact date if the subject discontinued from study due to lost to follow-up or withdrew consent or did not continue to the survival follow up phase.
- **New anti-cancer therapy:** OS will be analyzed regardless of whether new anti-neoplastic therapy is initiated. Death collected after the start of new anti-cancer therapy will be used for OS analysis.

12.5.1.2 Sensitivity and supplementary analyses

If the OS analysis (either interim or final) is statistically significant, supplementary analyses will be performed in the FAS, the hazard ratio and 95% confidence interval for OS will be obtained from:

- an unstratified and covariate unadjusted Cox model.
- a stratified and covariate adjusted Cox model including as covariates the following: gender, age groups (<65, ≥65 years), ECOG PS (0, 1), histology (squamous, non-squamous), smoking status (smoker, non-smokers, ex-smokers), race (Asian, other). A final list of covariates will be defined in the SAP.
- a sub group analysis to assess the homogeneity of the treatment effect across demographics and baseline characteristics will be performed. The following subgroups maybe considered: gender, age groups (<65, ≥65 years), ECOG PS (0, 1), histology (squamous, non-squamous), smoking status (smoker, non-smokers, ex-smokers), race (Asian, other), presence or absence of brain metastasis at baseline (as assessed investigator per RECIST 1.1) and PD-L1 expression (<1%, or 1-49%, or ≥50%). A final list of subgroups of interest will be defined in the SAP.

12.5.2 Other secondary endpoint(s)

12.5.2.1 Efficacy endpoint(s)

Part 1: Single Arm Run-in Part

The secondary efficacy endpoints are the following:

- Disease control rate (DCR) and progression free survival (PFS) by investigator assessment as per RECIST 1.1.

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated. Therefore, the analysis for Part 2 are not applicable.

The secondary efficacy endpoints are the following:

- Progression free survival (PFS) by investigator assessment as per RECIST 1.1.

- Disease control rate (DCR), duration of response (DOR), overall response rate (ORR) and time to response (TTR) by investigator assessment and BIRC as per RECIST 1.1.

Disease control rate (DCR)

DCR is defined as the proportion of subjects with a confirmed best overall response (BOR) of complete response (CR), partial response (PR) and stable disease (SD) according to RECIST 1.1 (see Appendix 1).

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

Participants who had never received one of the investigational drugs will be excluded from the DCR analysis.

Progression free survival (PFS)

The analysis in this section refer to the PFS as per local investigator assessment for Part 1.

PFS is defined as the time from the date of start of treatment (Part 1) to the date of the first documented progression according to RECIST 1.1, or death due to any cause. If a subject has no progression or death, the subject is censored at the date of last adequate tumor assessment. Definition of last adequate tumor assessment is provided in Appendix 1.

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

Participants who did not receive one of the investigational drugs will be excluded from the PFS analysis.

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), if the event occurred after two or more missing tumor assessments, or study treatment discontinuation before radiological progression or death. Clinical progression without objective radiological evidence will not be considered as documented disease 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 occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred), the date of enrollment will be used.

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

12.5.2.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented for the safety set for each part (overall for Part 1; and by treatment group for Part 2).

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:

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

Post-treatment period:

- starting at day 31 after the last administration of study treatment.

Safety summaries will primarily be based on all data from the on-treatment period. Following last administration of study treatment, adverse events (including serious adverse events) will be collected until 150 day from last dose of spartalizumab/placebo or 30 days from last dose of capmatinib whichever is longer in subjects receiving both investigational drugs. New anti-neoplastic therapies will be collected until subject's death or lost to follow-up. Following start of new anti-neoplastic therapy, only study treatment related adverse events will be collected. Select summaries of related adverse events may be produced for the combined on-treatment and post-treatment periods. Details will be specified in the SAP.

Adverse events

All information obtained on adverse events will be displayed for safety set.

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

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

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

The number (and percentage) of subjects with adverse events of special interest will be summarized.

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

All deaths and on-treatment deaths will be summarized.

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

Vital signs

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

Vital signs collected during on-treatment will be summarized. The number and percentage of subjects with notable vital sign values will be presented for the safety set. A listing of subjects with notable vital signs will be provided and value measure during the post-treatment follow up will be flagged in the listing. Notable vital sign values criteria will be specified in the SAP.

12-lead ECG

12-lead ECGs including PR, QRS, QT and QTcF intervals and heart rate will be obtained for each subject during the study. ECG data will be read and interpreted locally. The average of the ECG parameters at each assessment should be used in the analyses.

ECGs collected during on-treatment will be summarized. The number and percentage of subjects with notable ECG values will be presented for the safety set. A listing of subjects with notable ECGs will be provided and value measure during the post-treatment follow up will be flagged in the listing. Notable ECG values criteria will be specified in the SAP.

Clinical laboratory evaluations

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

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

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

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

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

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 post-baseline value.

12.5.2.3 Tolerability

Tolerability of study drug will be assessed by summarizing the number of and reasons for dose delays/interruptions and dose reductions. Dose intensity will also be tabulated by treatment group for each component of the study treatment.

12.5.2.4 Pharmacokinetics

All PK data analysis and PK summary statistics will be based on the INC-PAS and PDR-PAS. PK parameters summary statistics will be based on the INC-FPAS and PDR-FPAS.

Descritpive summary statistics of capmatinib and spartalizumab concentration data will beprovided 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 (see Table 12-1) will only be derived from the subjects in the FPAS (INC-FPAS and PDR-FPAS). Descriptive summary statistics, for the PK parameters, 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.

Table 12-1 Non-compartmental pharmacokinetic parameters

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

12.5.2.4.1 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%.

12.5.2.4.2 Population pharmacokinetic analysis

If data permit, a mixed-effects model may be applied to the spartalizumab and/or capmatinib concentration-time data to characterize spartalizumab and/or capmatinib exposure. If there are sufficient data for analysis, the details of the population pharmacokinetic analyses will be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report. Data from this and other studies may be pooled for analysis.

[redacted]

[redacted]

12.7 Interim analyses

Part 1: Single Arm Run-in Part

No formal interim analysis is planned for Part 1 of the study.

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated. The analysis for Part 2 are not applicable.

Progression free survival

One efficacy interim analysis for PFS is planned after approximately 145 PFS events out of 193 (i.e. at approximately 75% information fraction) have been documented. This analysis is expected to occur approximately 39 months after randomization of the first subject. The primary intent of this interim analyses is to report early outstanding efficacy results in terms of PFS if the pre-specified threshold for significance is crossed.

The interim analysis will only be carried out after all subjects have been randomized. A weighted log rank test using Fleming-Harrington class of weights will be used as a supplementary analysis to account for the possible delay effect in the capmatinib + spartalizumab arm. In addition as a supplementary analysis, if proportional hazard assumption is violated as a result of a delayed treatment effect, a stratified piecewise Cox regression analysis will be used to estimate the HR after the delay treatment effect.

An alpha spending function according to a two-look (Lan-DeMets) group sequential design with (O'Brien-Fleming) type stopping boundary (as implemented in East 6.4) will be used to construct the efficacy stopping boundaries (Lan and DeMets 1983).

The exact nominal p-value that will be needed to declare statistical significance at the time of interim analysis will depend on the number of the PFS events that have been observed at the interim and for the final analysis. The observed p-value at the time of primary and final will be compared to the recalculated boundary.

If the number of PFS events at the interim analysis is exactly 145 then significant results will be obtain if the p-value < 0.0096 (or equivalent of the HR < 0.662). Similarly assuming 145 events have been previously observed at the time of the interim analysis and if there are exactly 193 PFS events at the final PFS analysis then significant results will be obtain if the p-value < 0.022 (or equivalent of the HR < 0.735). Note that the significance boundaries were chosen assuming no delay treatment effect.

The interim analysis for PFS will be performed by an independent external statistician (not involved with the conduct of the study). This will include the PFS analysis plus other critical efficacy endpoints and safety data. The results will be made available to the DMCs who will then make recommendations to Novartis (see Section 10.2.2).

The DMC recommendation at the interim PFS analysis will be based on whether the pre-specified efficacy threshold for primary endpoint PFS by BIRC was met and will also take into account PFS results by local investigator assessment. The details on criteria used will be provided in the DMC charter.

If the DMC recommendation is to consider making the unblinded results available, key Novartis personnel will review the (unblinded) interim data and make the final decision on what steps to take. Full details of this decision-making process including who will have access to the unblinded results will be specified in the DMC Charter.

The estimated timing of the interim and final PFS analyses based on current design is summarized in Table 12-2.

Table 12-2 Estimated timelines for interim and final PFS analyses an simulated power

Analysis	Analysis time (months after randomization of the first patient)	# PFS events (information fraction)	Cumulative PFS power against a hazard ratio of 1 for first 3 months and a hazard ratio of 0.55 after 3 months
Interim	39	145 (75%)	53.6%
Final	59	193 (100%)	85.3%
Calculations using EAST 6.4, Seed =12345, Number of simulations =10,000			

Overall survival (OS)

Interim analyses for OS are planned at the time of the interim and final analysis for PFS (provided PFS is significant), and when approximately 167 deaths are observed. A hierarchical testing procedure will be adopted and the statistical test for OS will be performed only if the primary efficacy endpoint PFS is statistically significant.

A maximum of four analyses are planned for OS:

1. At the time of the interim analysis for PFS (provided PFS is significant)
2. At the time of the final analysis for PFS (provided that either interim or final PFS analysis is significant)

3. At an interim analysis for OS when approximately 167 deaths (expected approximately 74 months after randomization of the first subject) in case the time gap between the final analyses for PFS and for OS is longer than 1 year
4. At a final analysis for OS when approximately 197 deaths (expected approximately 126 months after the randomization of the first subject).

An alpha spending function according to a four-look (Lan-DeMets) group sequential design with (O'Brien-Fleming) type stopping boundary (as implemented in East 6.4) will be used to construct the efficacy stopping boundaries (Lan and DeMets 1983). This controls 2.5% overall level of significance across the repeated testing of the OS hypotheses in the interim and the final analyses (Glimm et al 2010).

The trial allows for an early significance claim for efficacy for a superior OS result, provided the primary endpoint PFS has already been shown to be statistically significant favoring capmatinib in combination with spartalizumab arm. Further, the exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of deaths that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.

At the time of final PFS analysis, both PFS and interim OS analyses will be performed by the Sponsor's clinical team. Investigators and subjects will remain blinded to study treatment (unless OS reaches significance at any of the PFS analyses) and all subjects will continue to be followed for OS until study closure.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Part 1: Single Arm Run-in Part

No formal statistical power calculations to determine sample size were performed for this part of the study.

Approximately 30 subjects will be treated in Part 1 of the study. Table 12-3 shows the probability to detect a significant effect under different true ORR i.e. Probability to have ORR ≥ 55% and the lower bound of the 95% CI > 35%. If the true ORR is 67% there is 91.7% probability that the single arm run-in part will be declared a success.

Table 12-3 Design operating characteristics

True ORR	N	Minimum number of responses to declare success	ORR (95% CI)	Probability to reject H0
55%	30	17	56.7% (37.4 - 74.5)	50.2%
60%				71.5%
67%				91.7%

Part 2: Randomized Part

Following the study enrollment halt during Part 1, Part 2 will not be initiated.

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

Based on available data from the phase II single arm study CINC280A2201 (treatment-naive METΔex14 mutated, Cohort 5b), the median PFS in the capmatinib + placebo arm is expected to be around 10 months. Ignoring delayed treatment effect, it would be expected that the response to capmatinib when combined with spartalizumab would result in a hazard ratio of 0.55 (which corresponds to an increase in median PFS to 18.182 months under the exponential model assumption).

Given knowledge of a potential delayed treatment effect with IO compounds, it is hypothesized that there will be no difference between treatment arms until 3 months after the randomization date for PFS. Therefore, it is assumed that the HR between the groups will be equal to 1 for the first 3 months. Thereafter, exponential survival distributions are assumed, with an HR of 0.55. This will result in an overall HR=0.636 (Kalbfleisch and Prentice 1981) at the time of the final PFS analysis (given the assumed 3 month delayed treatment effect, this equates to median PFS of 15.73 and 10 months in the capmatinib + spartalizumab and capmatinib + placebo, respectively).

In order to ensure at least cumulative 85% power for PFS to test the null hypothesis: PFS hazard ratio = 1, versus the specific alternative hypothesis: overall PFS hazard ratio = 0.636, using the assumptions for HR=1 for the first 3 months and HR=0.55 thereafter, it is calculated that a total of 193 PFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, subjects randomized to the two treatment arms in a 2:1 ratio, and a 2-look group sequential design with a Lan-DeMets (O'Brien and Fleming) using information fractions of 0.75 and 1.

The total of approximately 193 PFS events targeted for the final PFS analysis represent a large percentage of the subjects randomized in the Part 2 of the study (80.4%).

Given the above assumptions, it is estimated that the 193rd PFS event will be observed approximately 59 months after first subject randomized in the study.

Assuming that enrollment will continue for 34 months at a uniform rate of 7 subjects per month, a total of 240 subjects will need to be randomized to observe the targeted 193 PFS events at about 59 months after the randomization date of the first subject. Then assuming losses to follow-up for PFS of 5% per year, the required sample size of the study is 240 randomized subjects in a 2:1 ratio (160 subjects in the capmatinib plus spartalizumab arm, 80 subjects in the capmatinib plus placebo arm). These calculations were made using the software package East 6.4.

12.8.2 Key secondary objective

Following the study enrollment halt during Part 1, Part 2 will not be initiated. The analysis and statistical methods for Part 2 are not applicable.

Part 2: Randomized Part

OS, as the key secondary variable, will be formally statistically tested, provided that the primary endpoint PFS is statistically significant. The hypothesis to be tested and the details are provided in Section 12.5.1.

Based on available data from the phase II single arm study CINC280A2201 (treatment-naive METΔex14 mutated, Cohort 5b), the median OS in the capmatinib + placebo arm is expected to be around 20 months. It would be expected that the capmatinib in combination with spartalizumab response would result in a hazard ratio of 0.65 (which corresponds to an increase in median OS to 30.769 months under the exponential model assumption).

In order to ensure at least 80% power for OS to test the null hypothesis: OS hazard ratio = 1, versus the specific alternative hypothesis: OS hazard ratio = 0.65, it is calculated that a total of 197 deaths need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, subjects are randomized to the two treatments in a 2:1 ratio and a four-look group sequential design with a Lan-DeMets (O'Brien and Fleming) alpha spending function using information fractions of 0.492, 0.741, 0.848, 1.

The type I error probability will be controlled by using a separate Lan-DeMets (O'Brien and Fleming) alpha spending function independent of the one used for the primary efficacy analysis of PFS at 2.5% level of significance. This guarantees the protection of the overall level α = 2.5% across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses (Glimm et al 2010).

Based on the same number of subjects that are planned to be enrolled in the Part 2 of this study to provide sufficient power for the primary endpoint (i.e. 240 subjects), and assuming losses to follow-up for OS of 5% per year, it is estimated that these 197 deaths will be observed approximately 126 months after the randomization date of the first subject. Therefore, the cut-off date for the third interim analysis of OS, if performed, would be approximately 15 months after the cut-off date for the final analysis of PFS; and the cut-off date for the final OS analysis will be approximately 67 months after the cut-off date for the final analysis of PFS. These calculations were made using the software package East 6.4.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the 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 (see Section 9.2.1) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT, etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local level laws and regulations, sites may discuss modifications to these requirements with Novartis:

- Thank You letter
- Plain language trial summary – after CSR publication

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

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16 Appendices

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

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Glossary

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

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).

This document will not address the use of RECIST 1.1 in glioblastoma multiforme (GBM), studies in adjuvant setting or immunotherapy.

The efficacy assessments described in Section 16.1.2 and the definition of best response in Section 16.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.1.3.2 is summarizing the “time to event” variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 16.1.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.1.2 Efficacy assessments

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

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

16.1.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.1.3.2.9.

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 10mm size, and can be assessed using calipers.
  - Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
  - Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
  - Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

16.1.2.3 Baseline documentation of target and non-target lesions

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

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

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
3. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.1.2.2).

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	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

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

16.1.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.1.3.2.9 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.1.3.1 Best overall response

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

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

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

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

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 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 central blinded review 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 16.1.3.2.6. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

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

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

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
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 16.1.3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

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

16.1.4.5.3 Incomplete dates for last known date patient alive or death

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

16.1.4.5.4 Non-target lesion response

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

16.1.4.5.5 Study/project specific programming

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

16.1.4.5.6 Censoring reason

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

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 16-5)
- Death due to reason other than underlying cancer
- 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.

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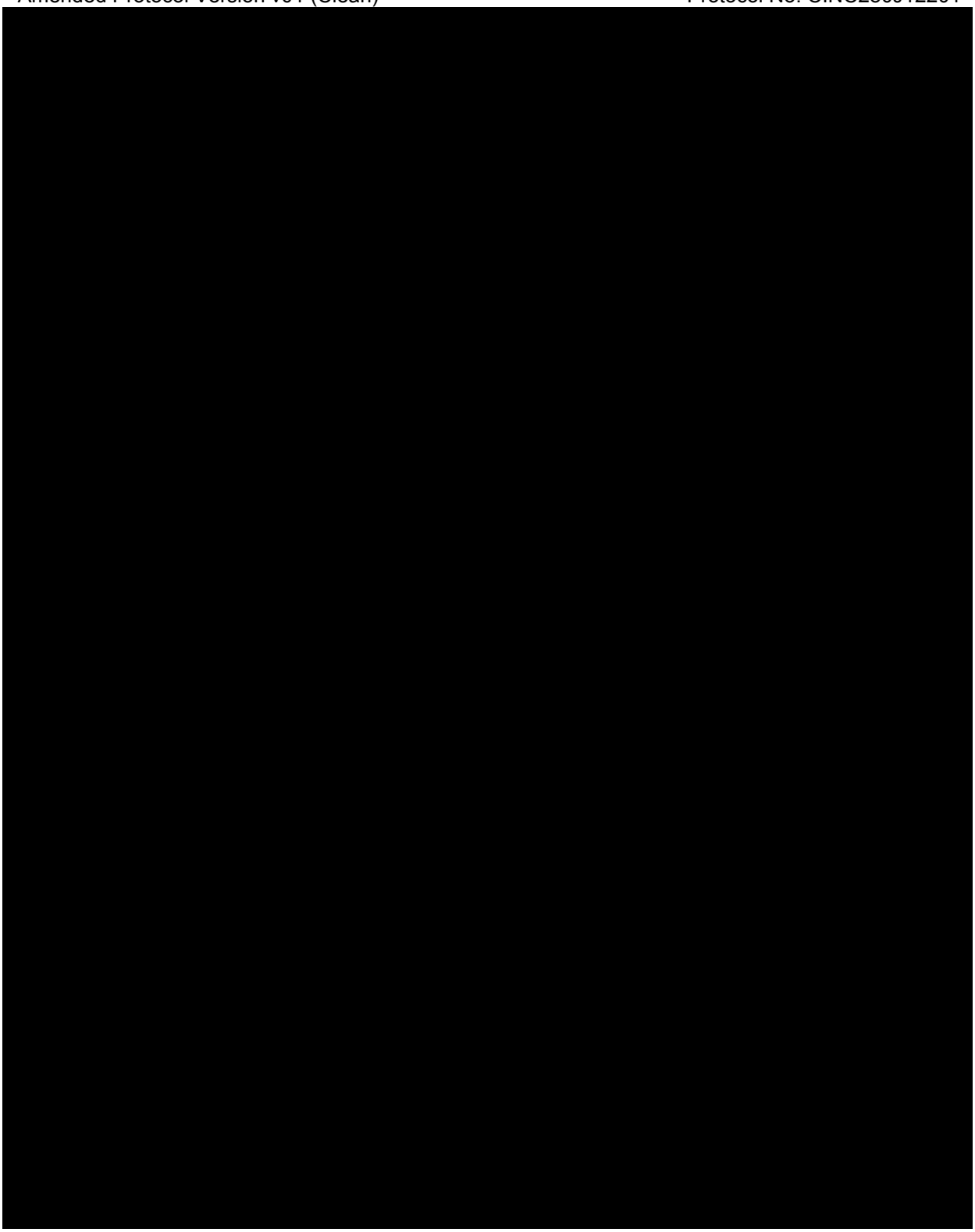

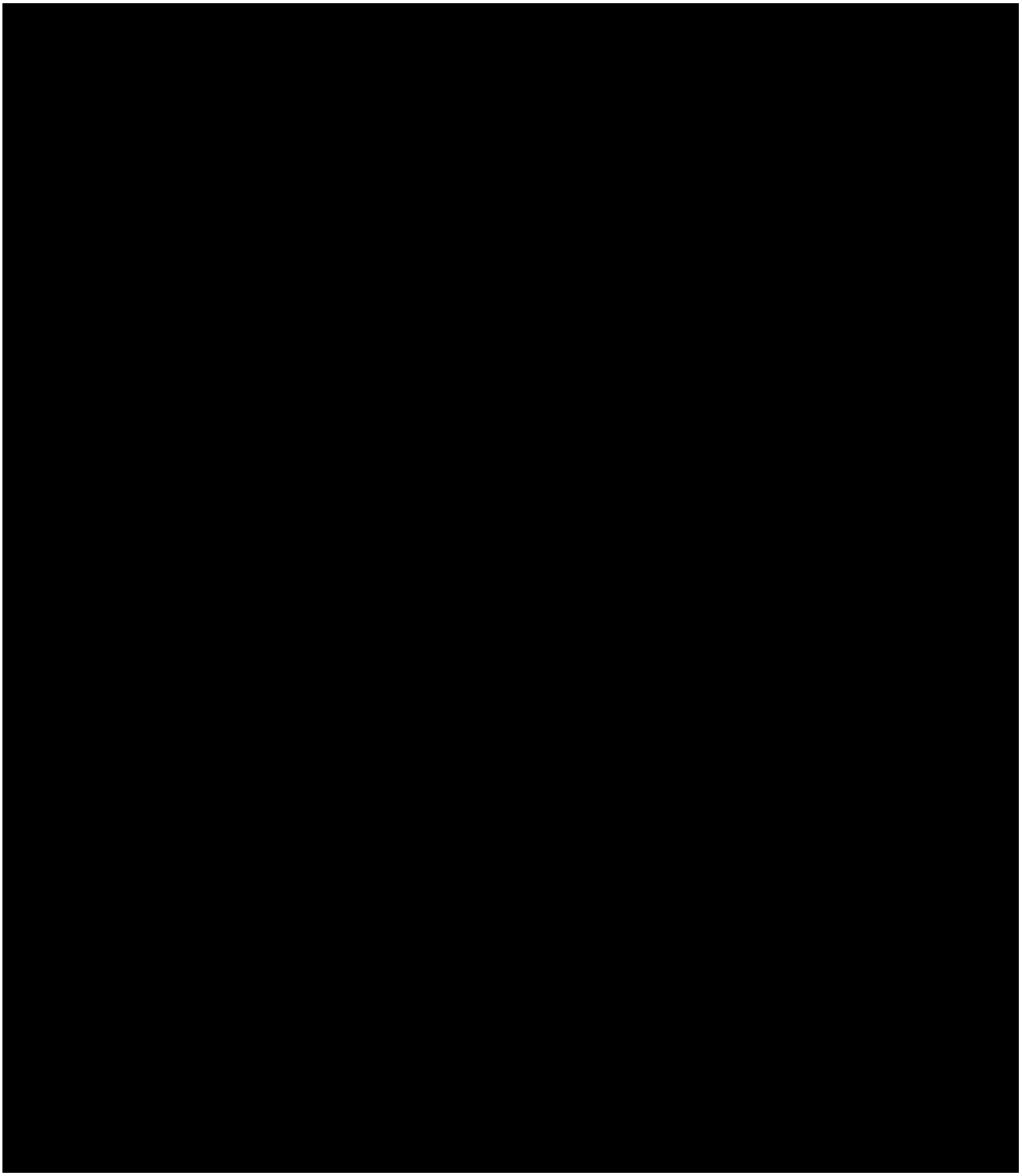

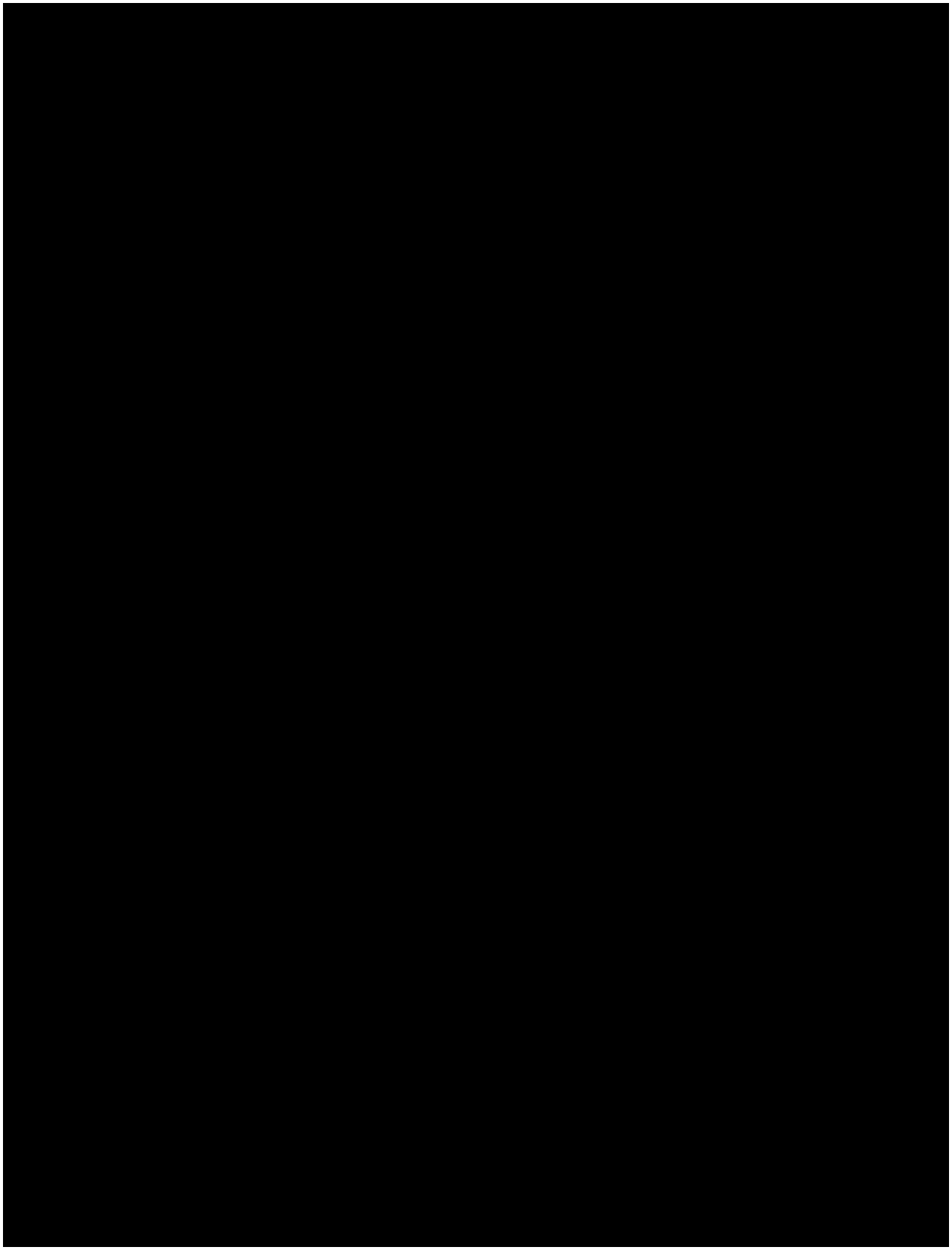

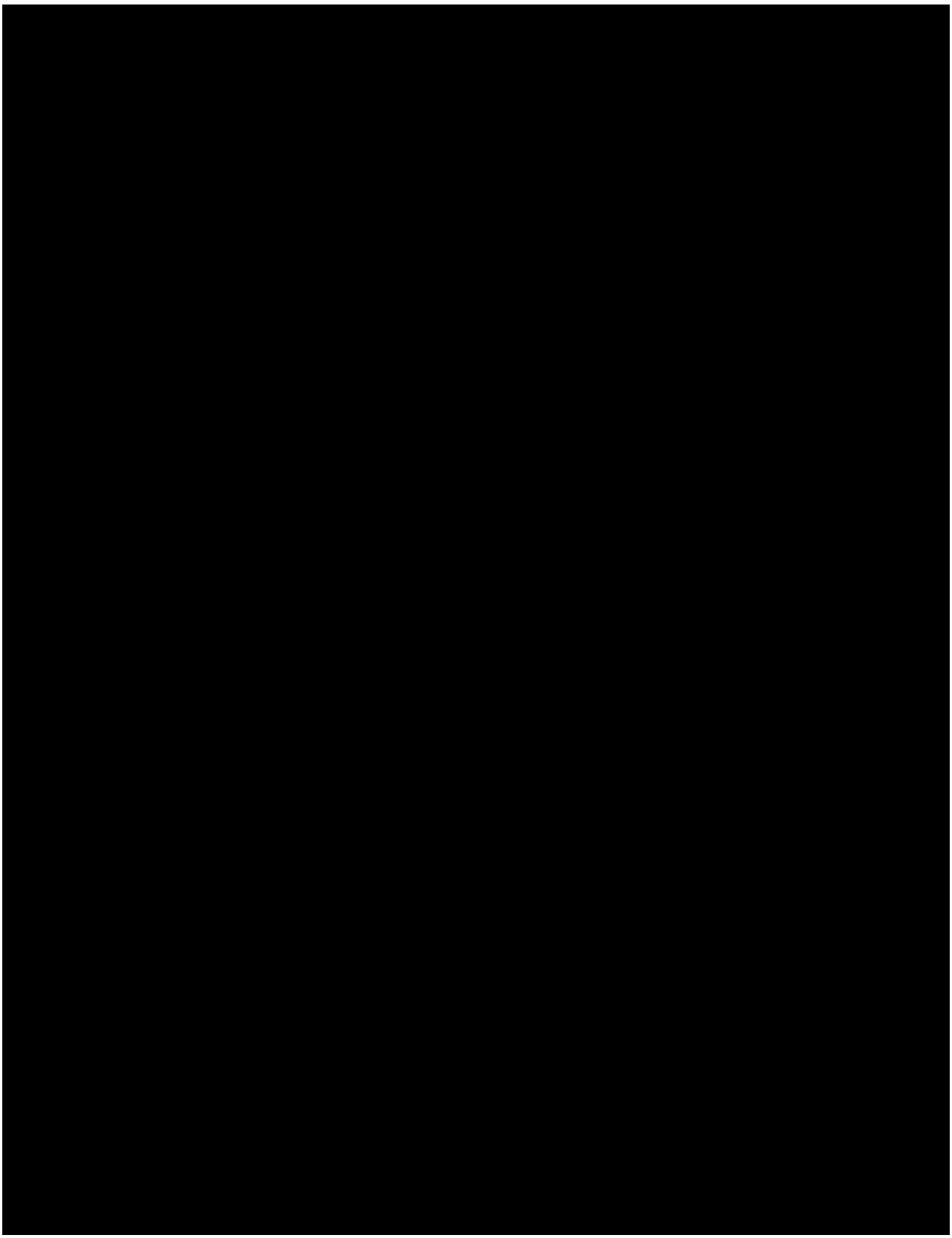

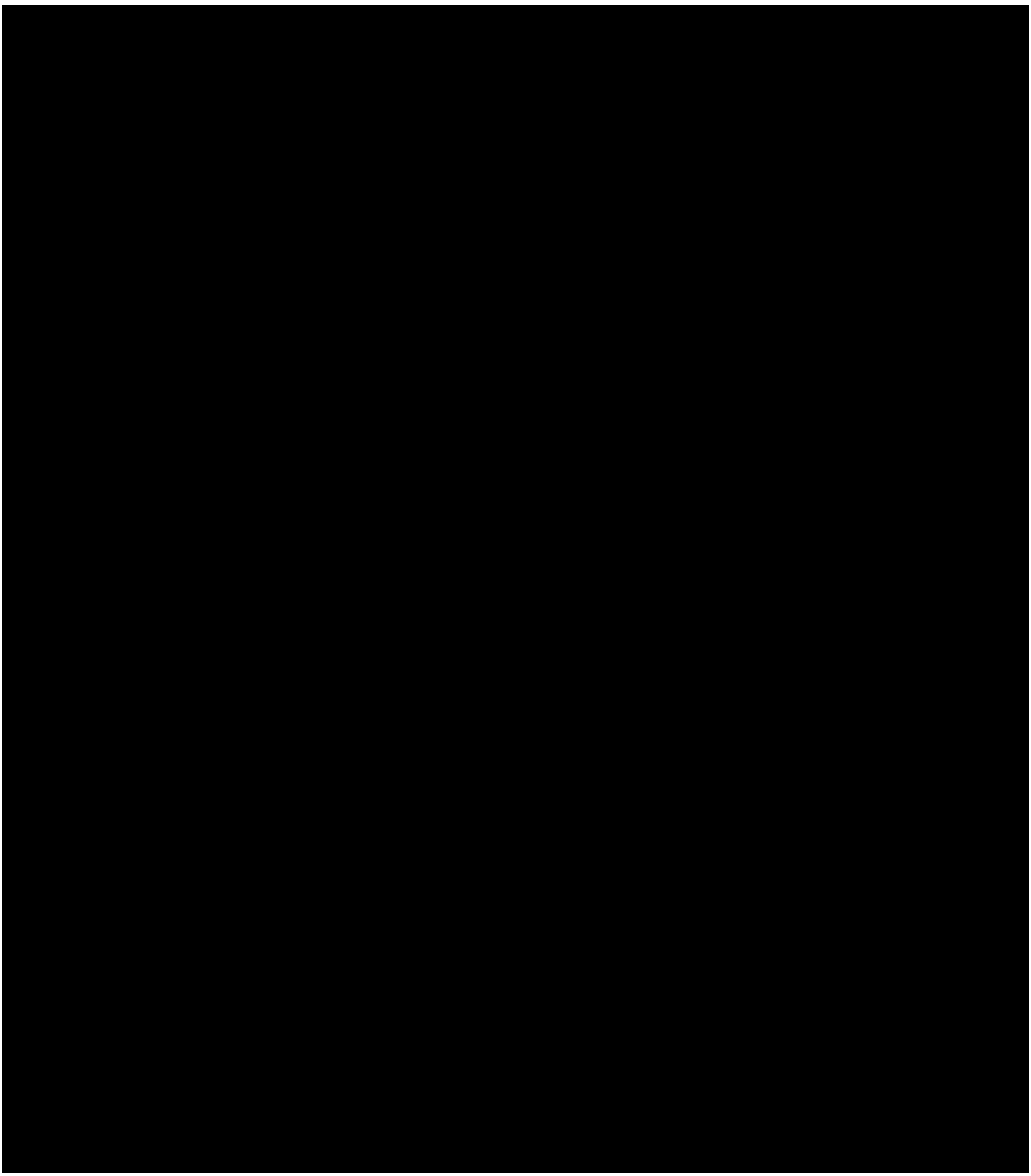

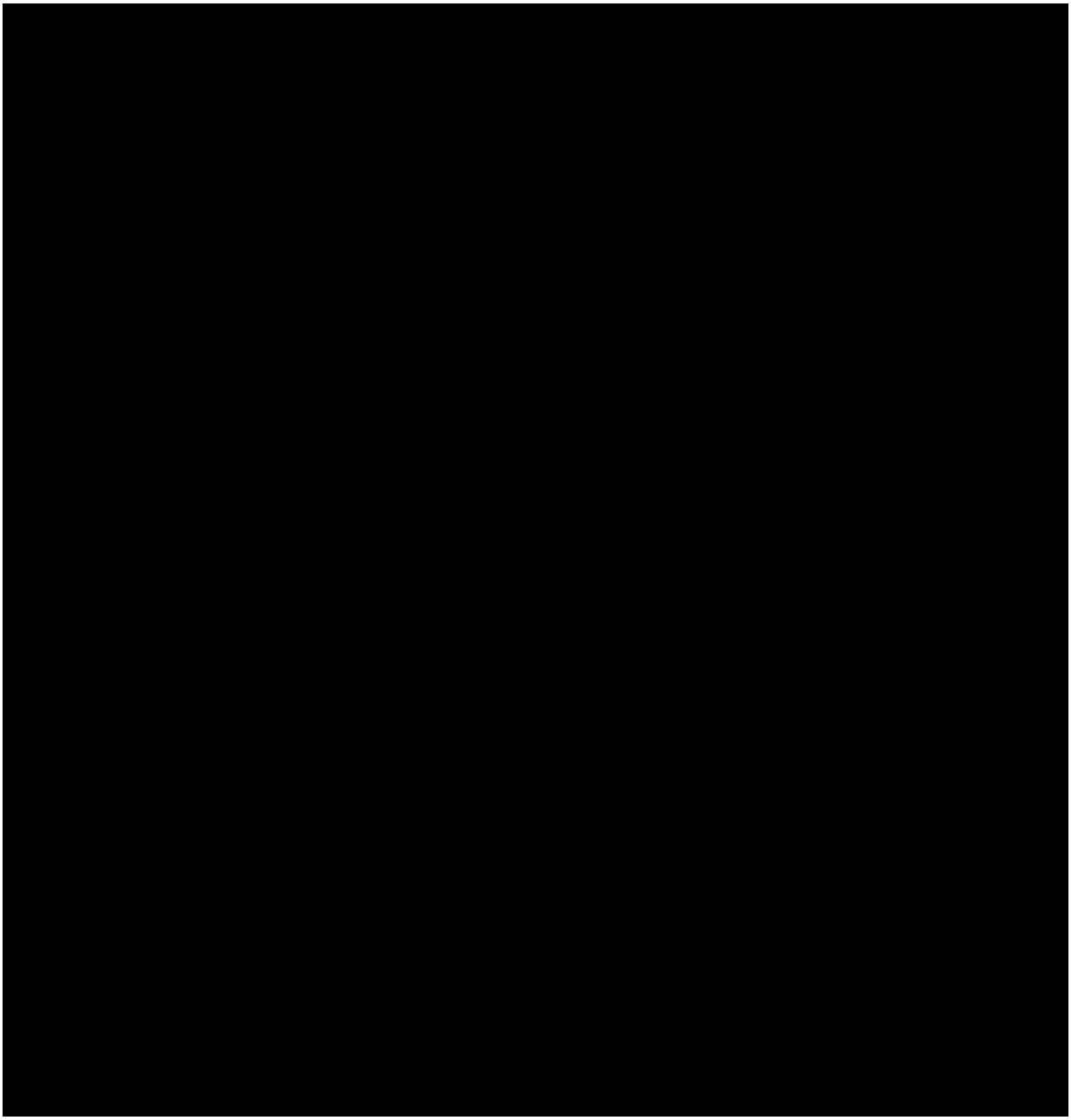

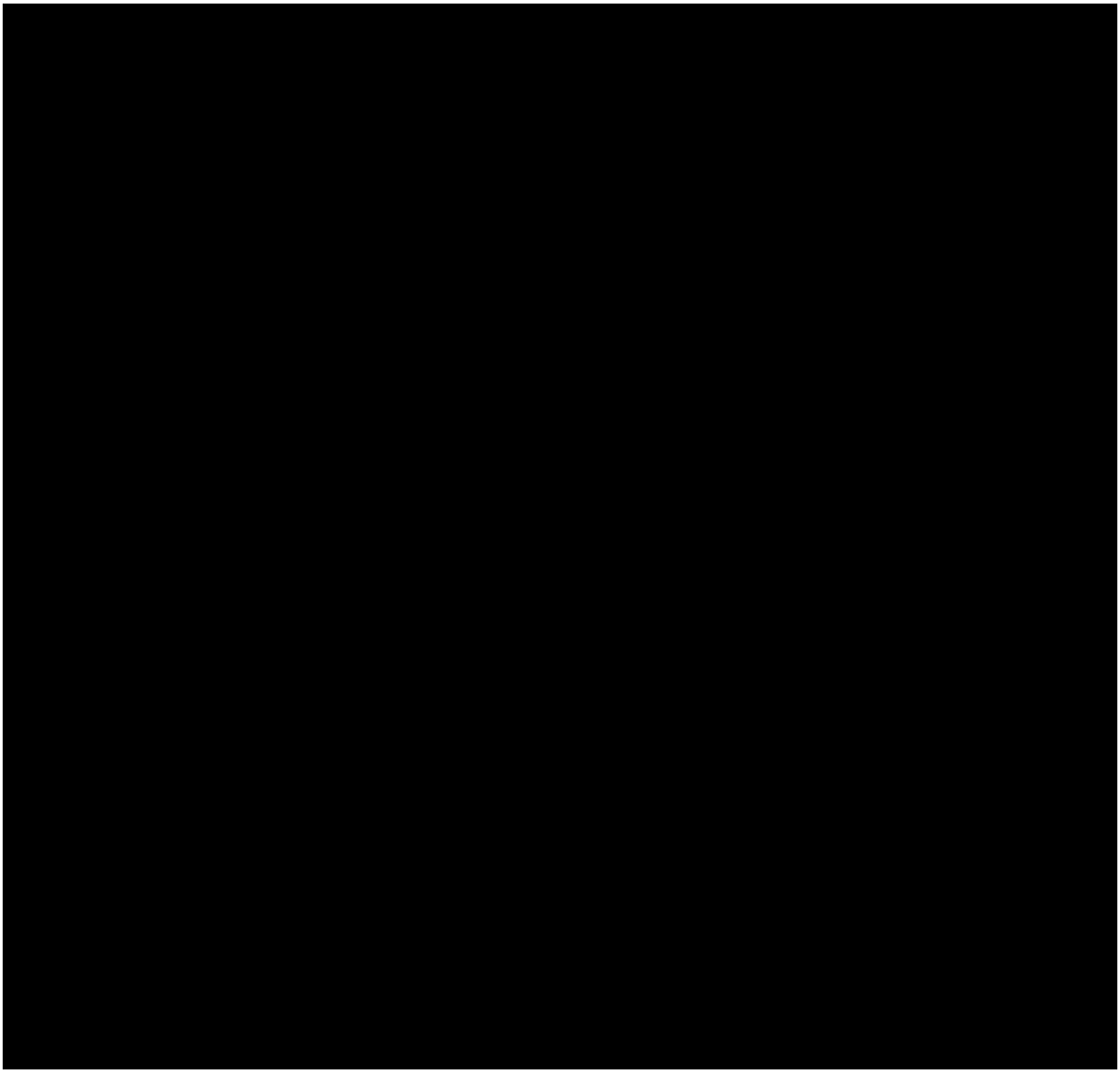

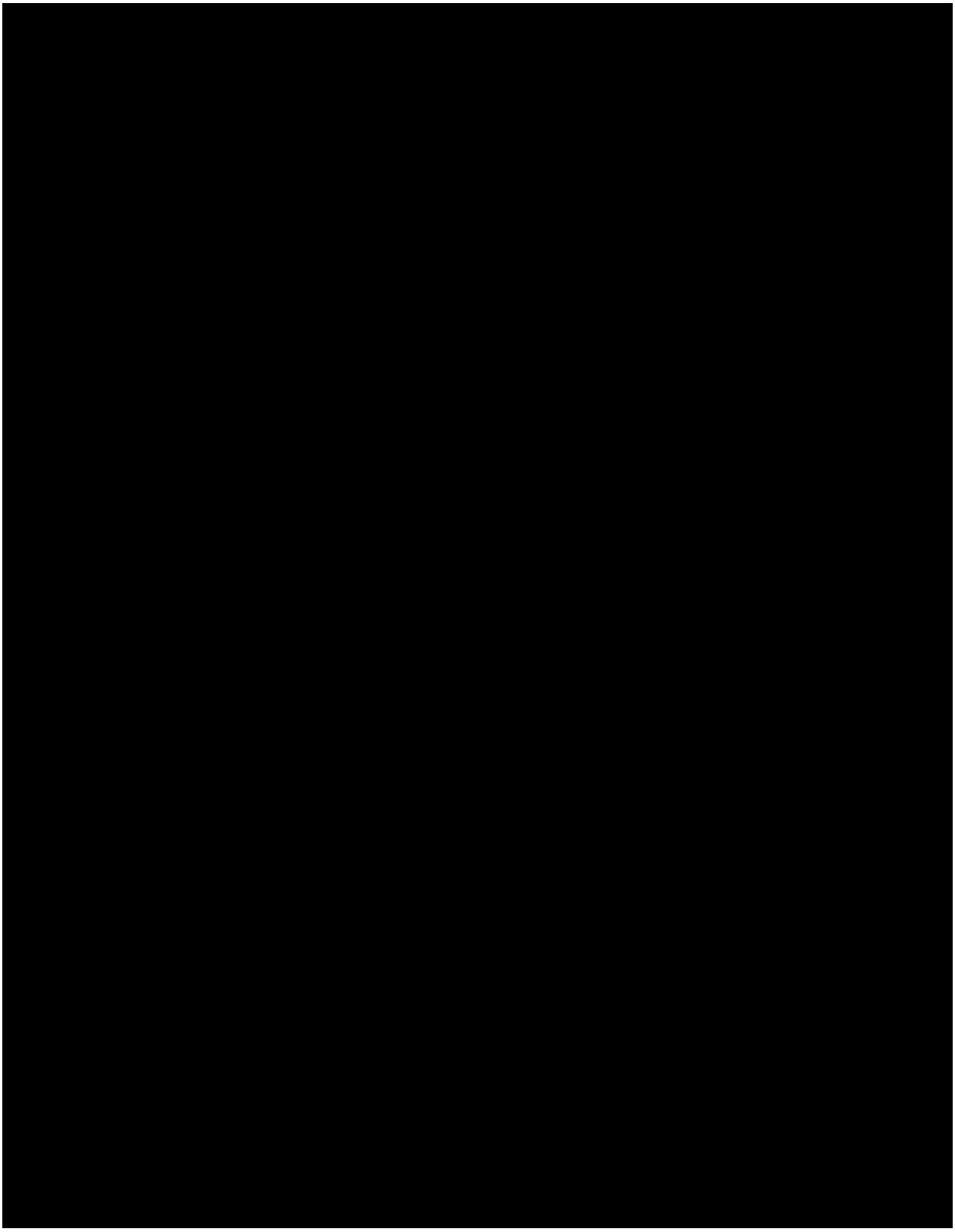

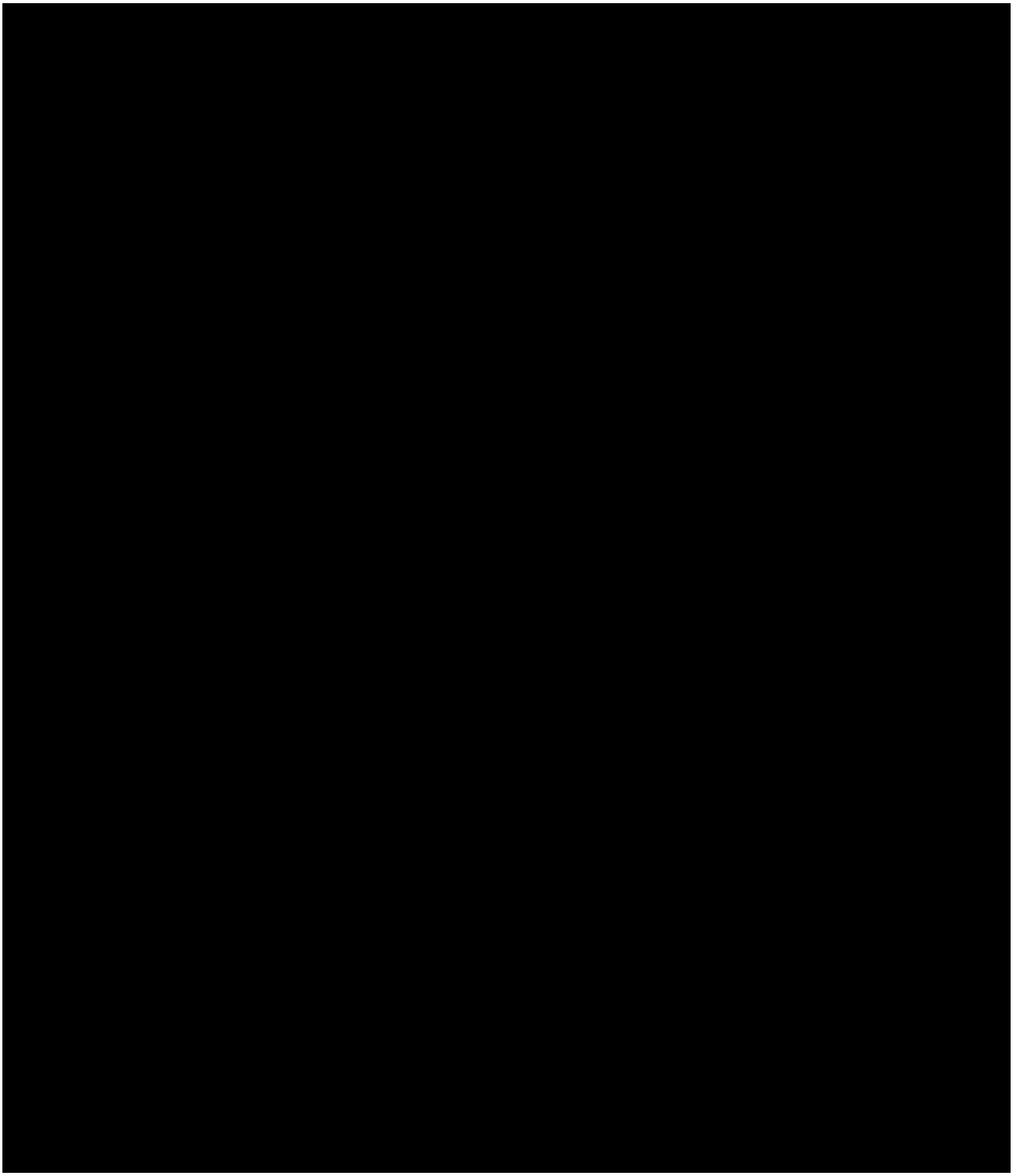

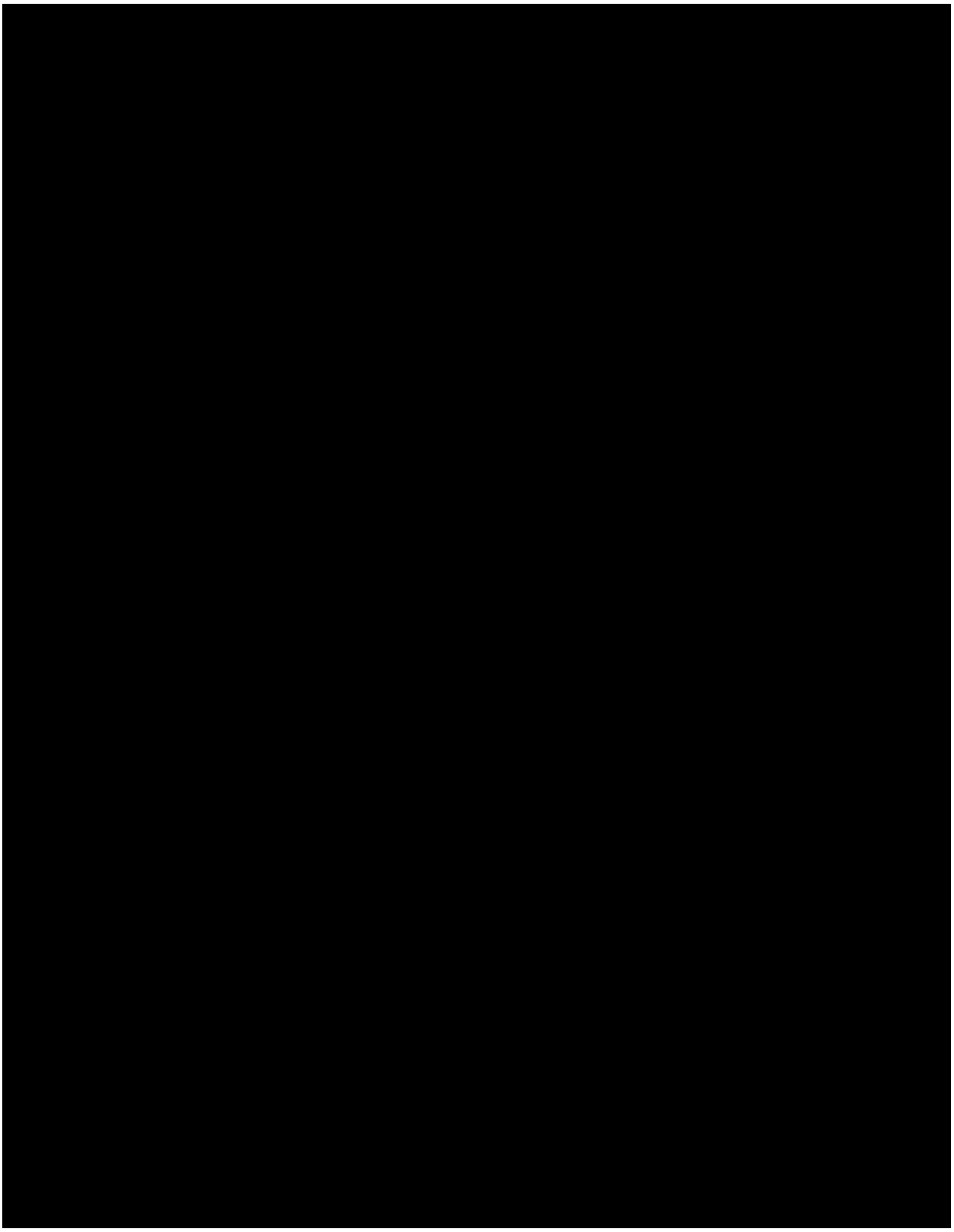

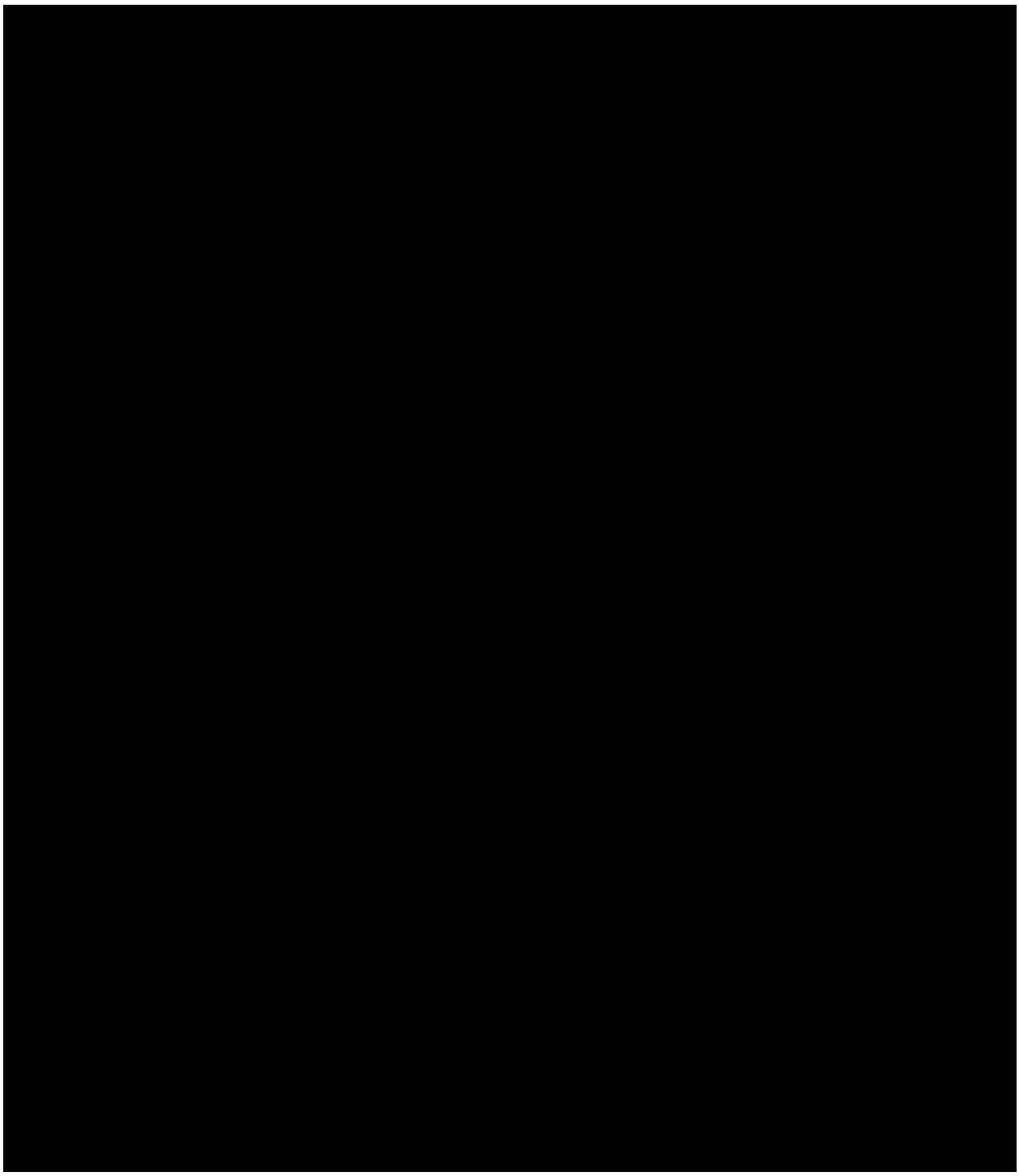

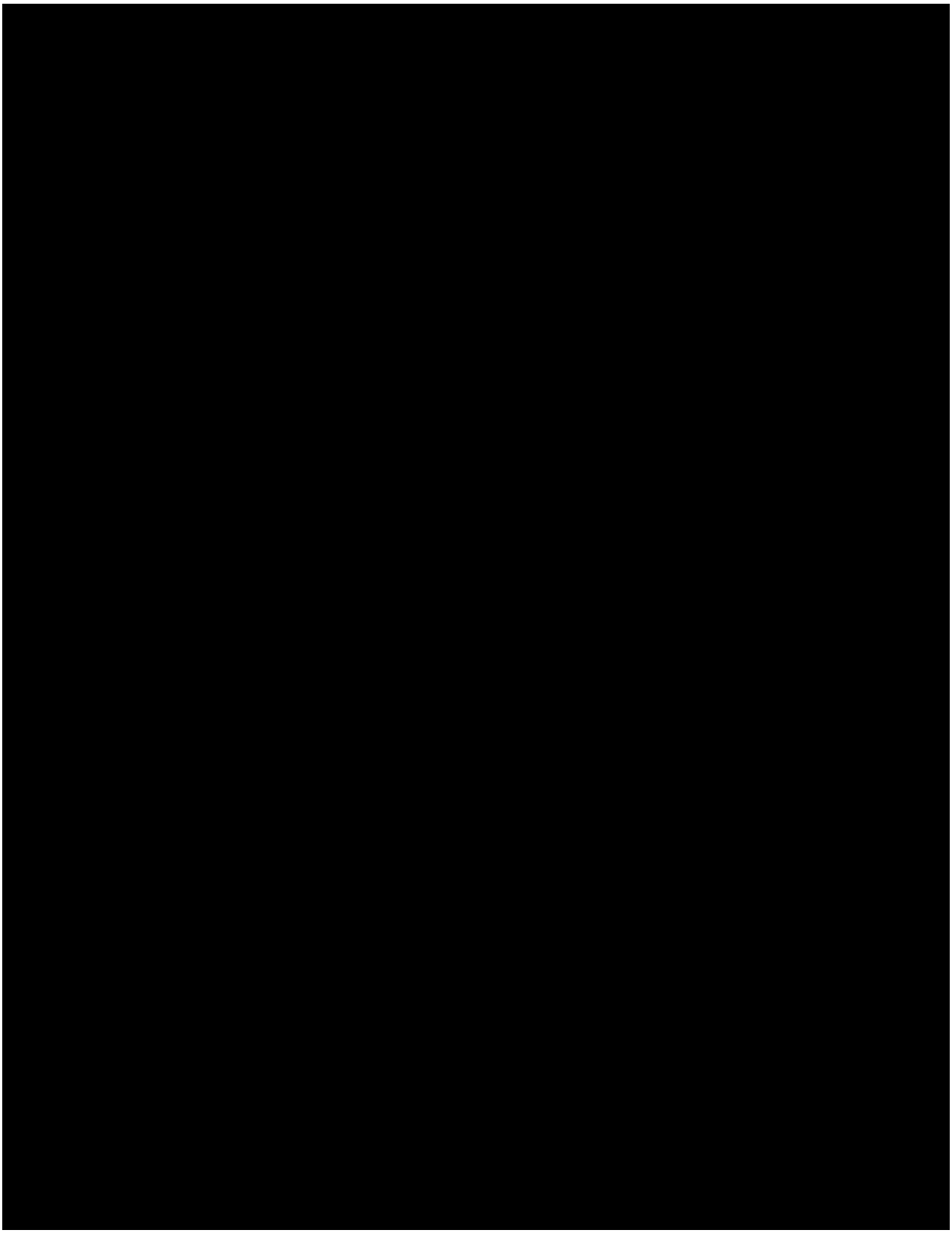

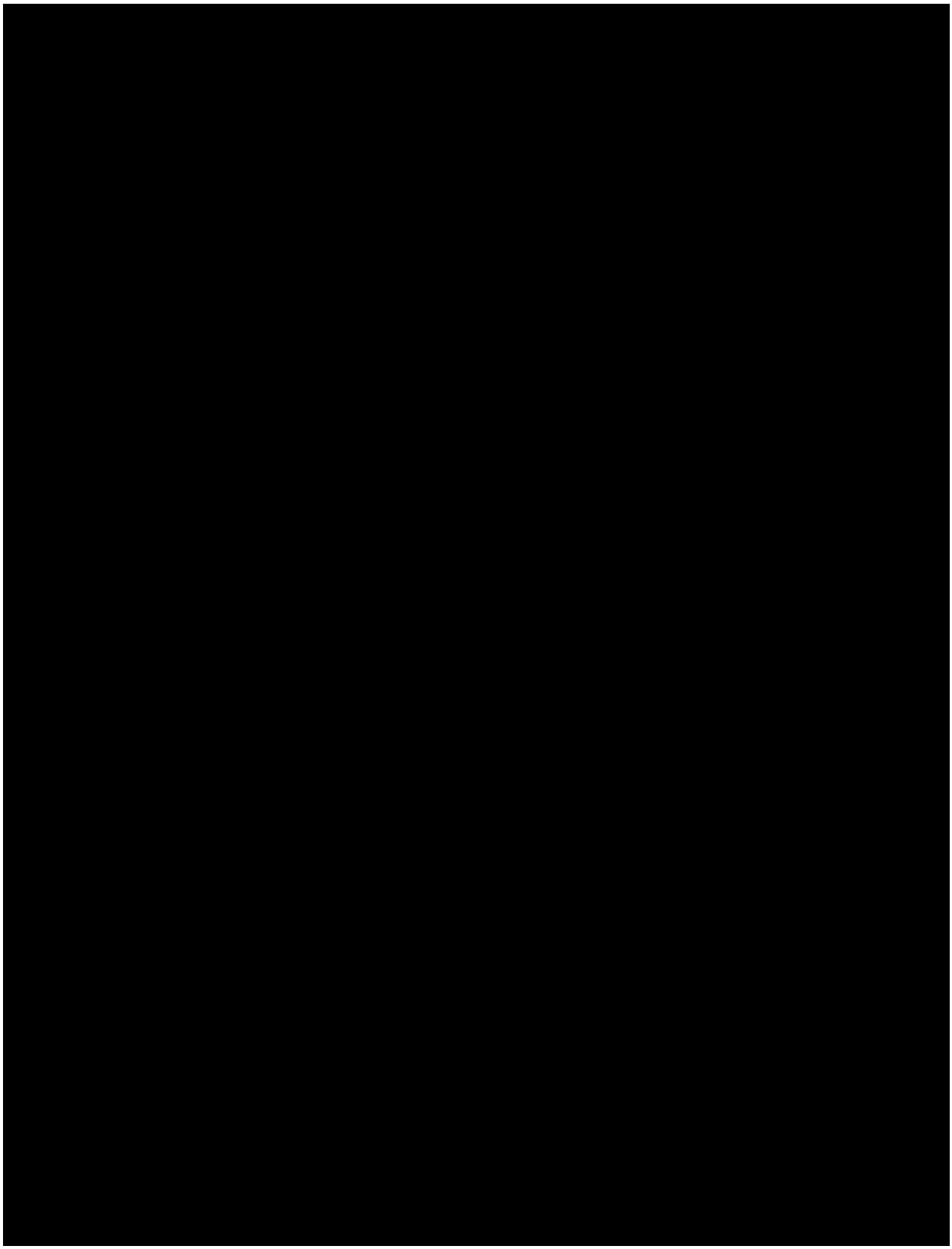

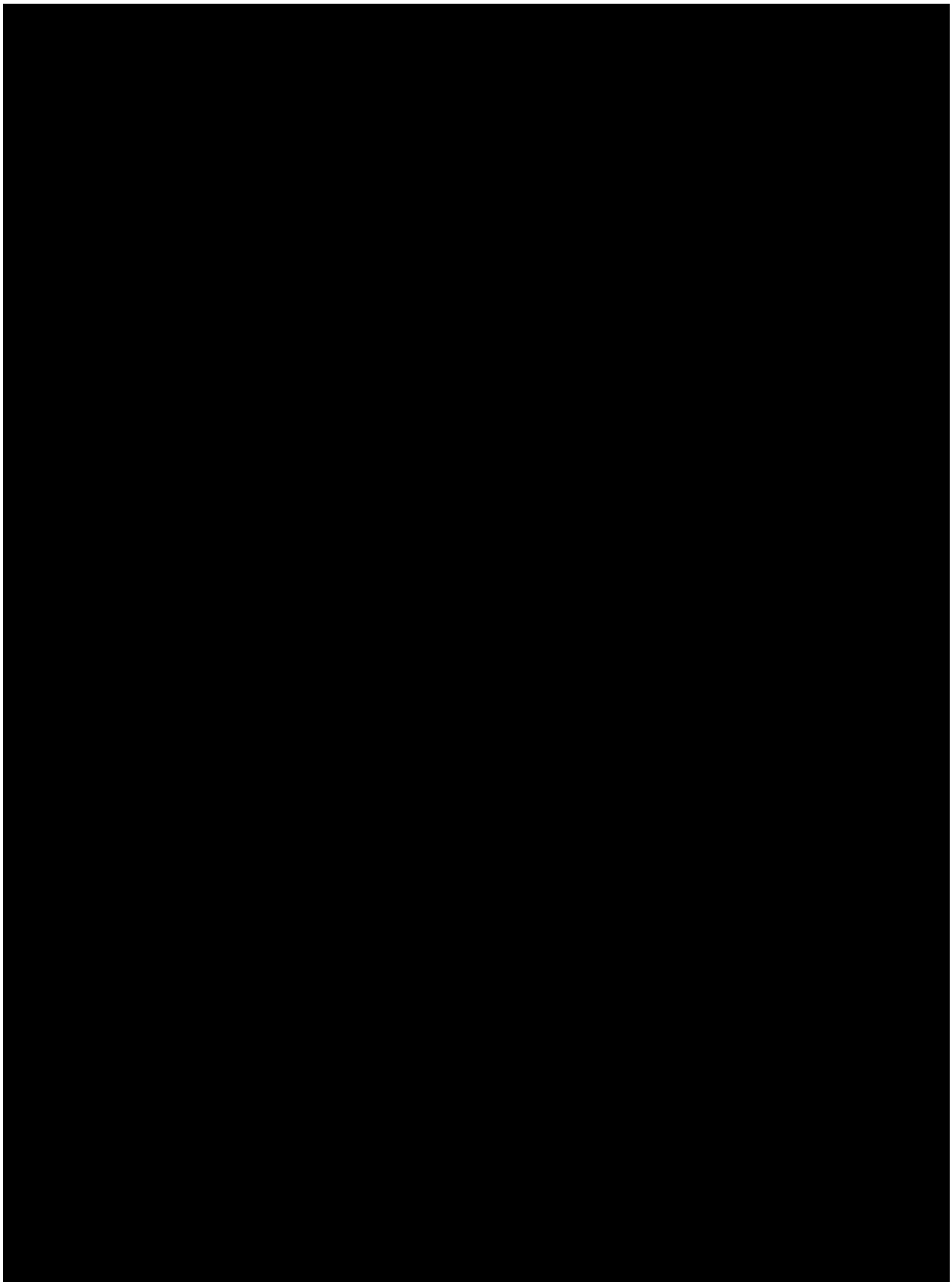

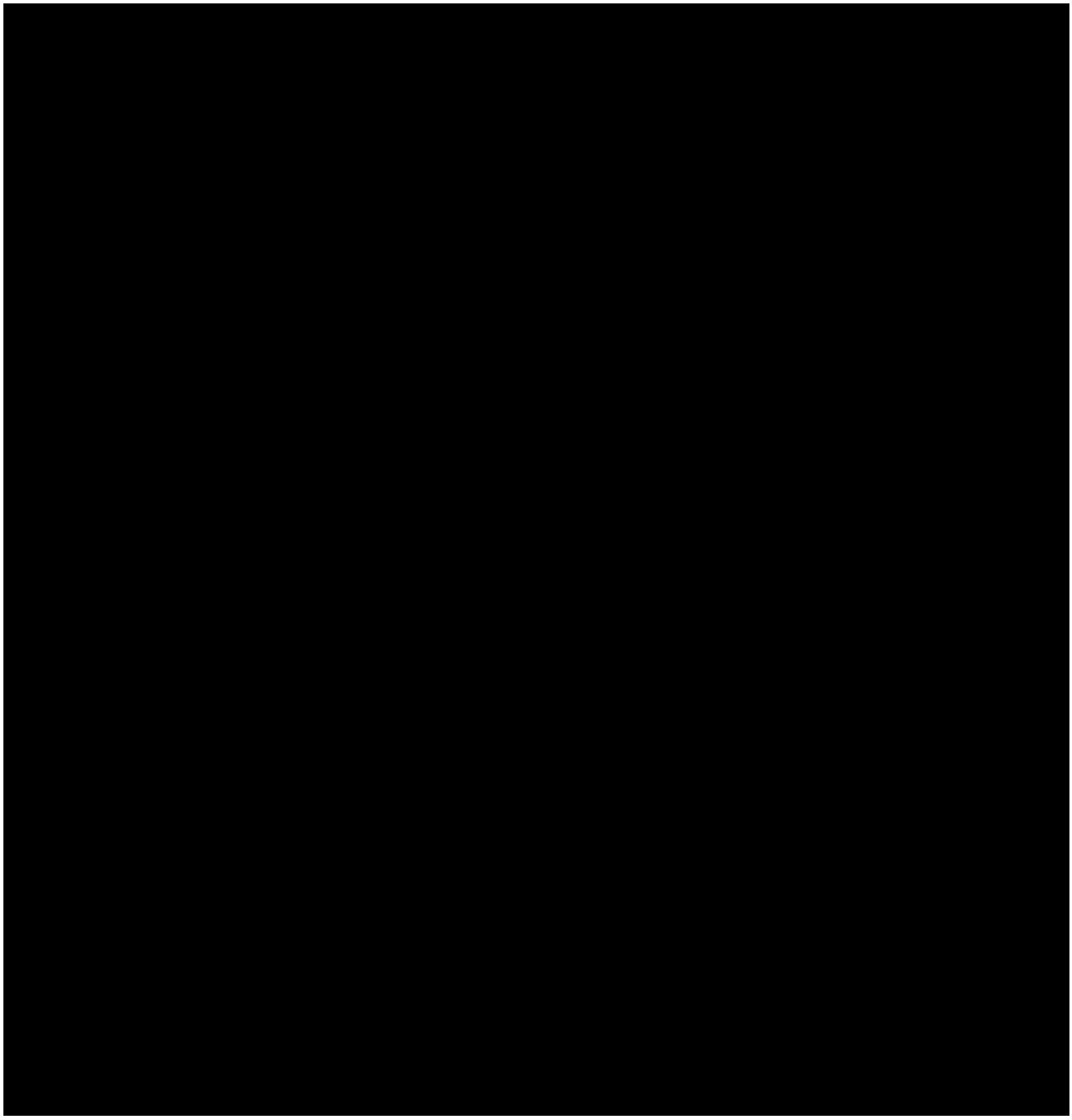

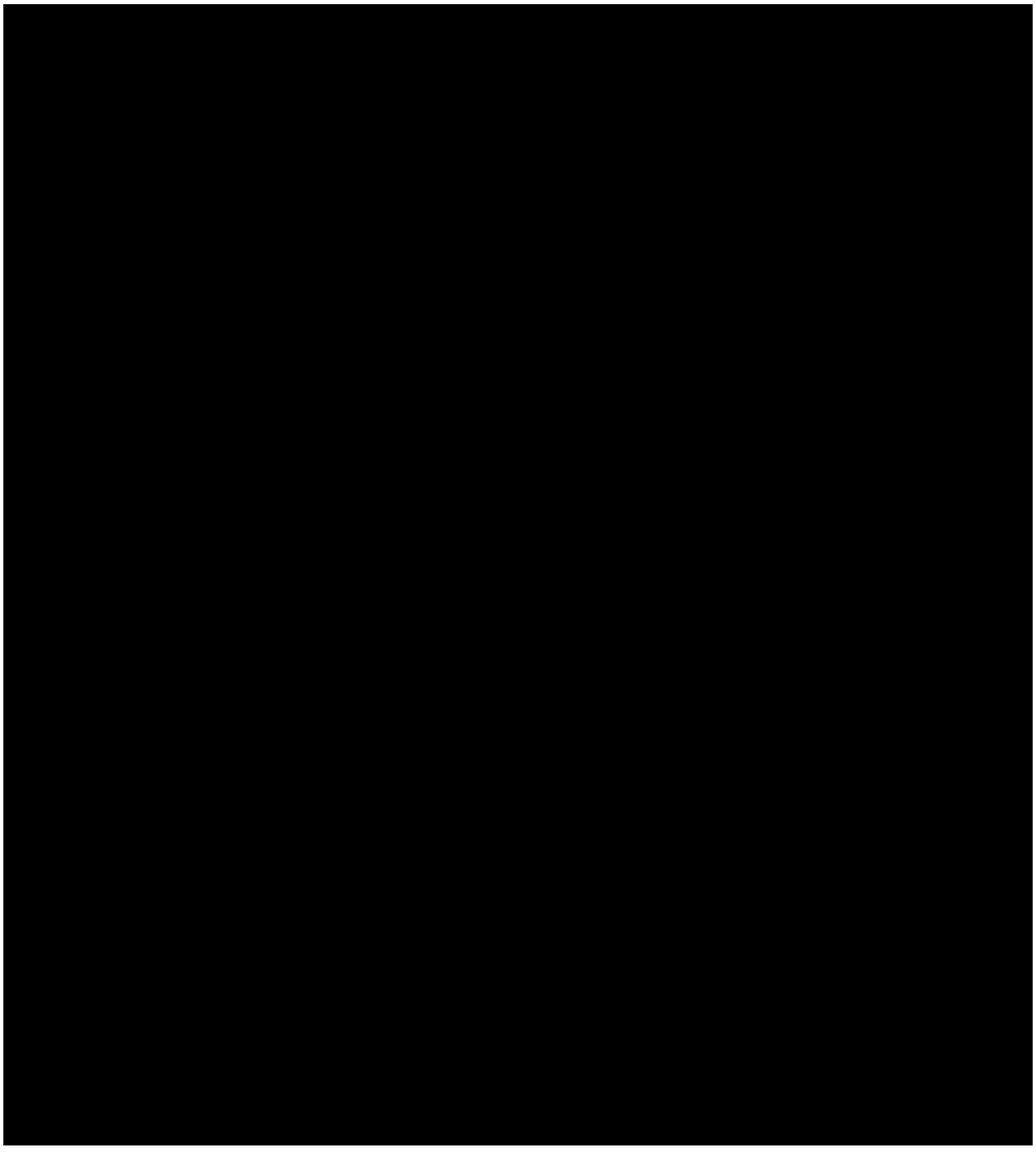

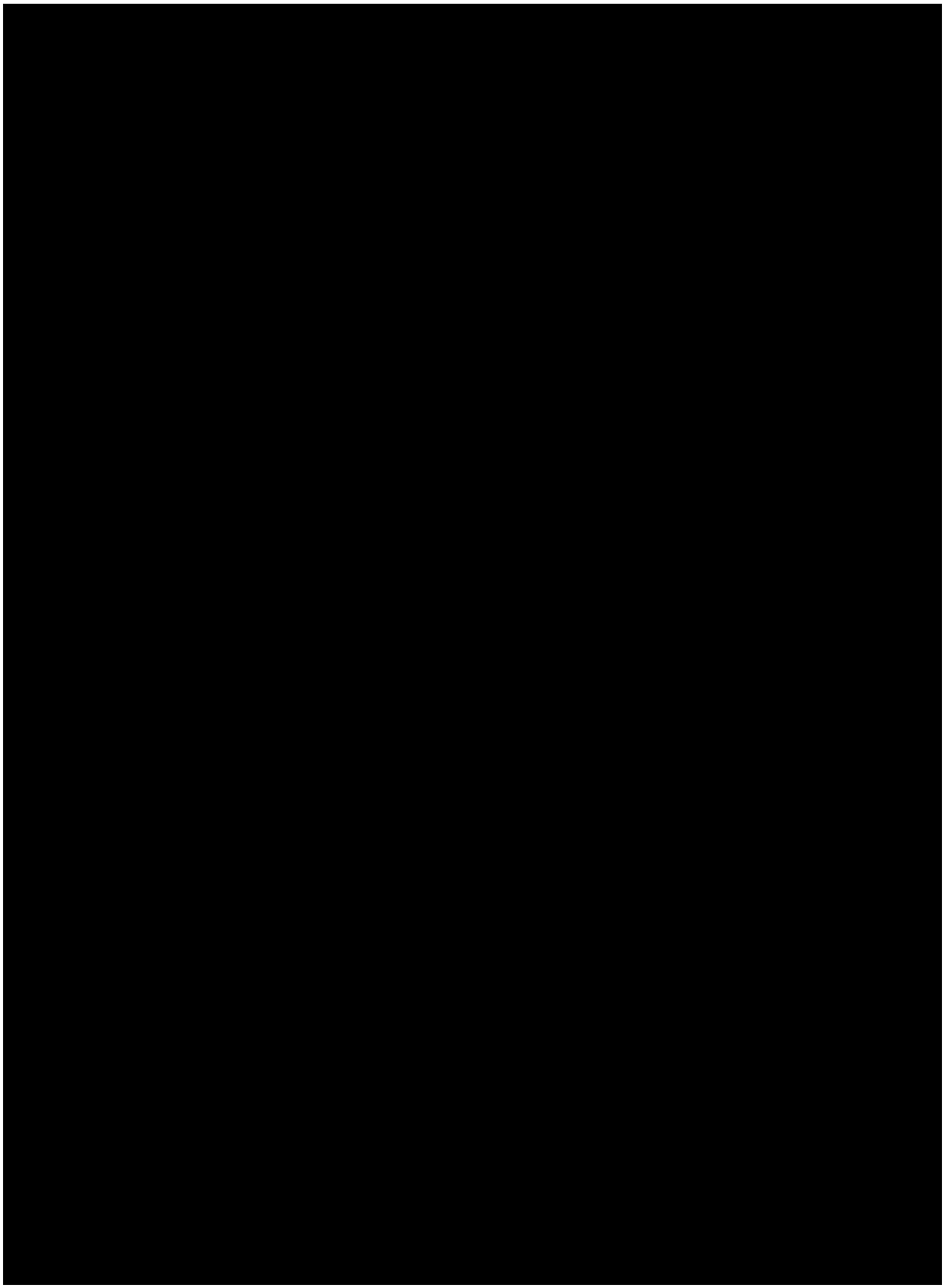

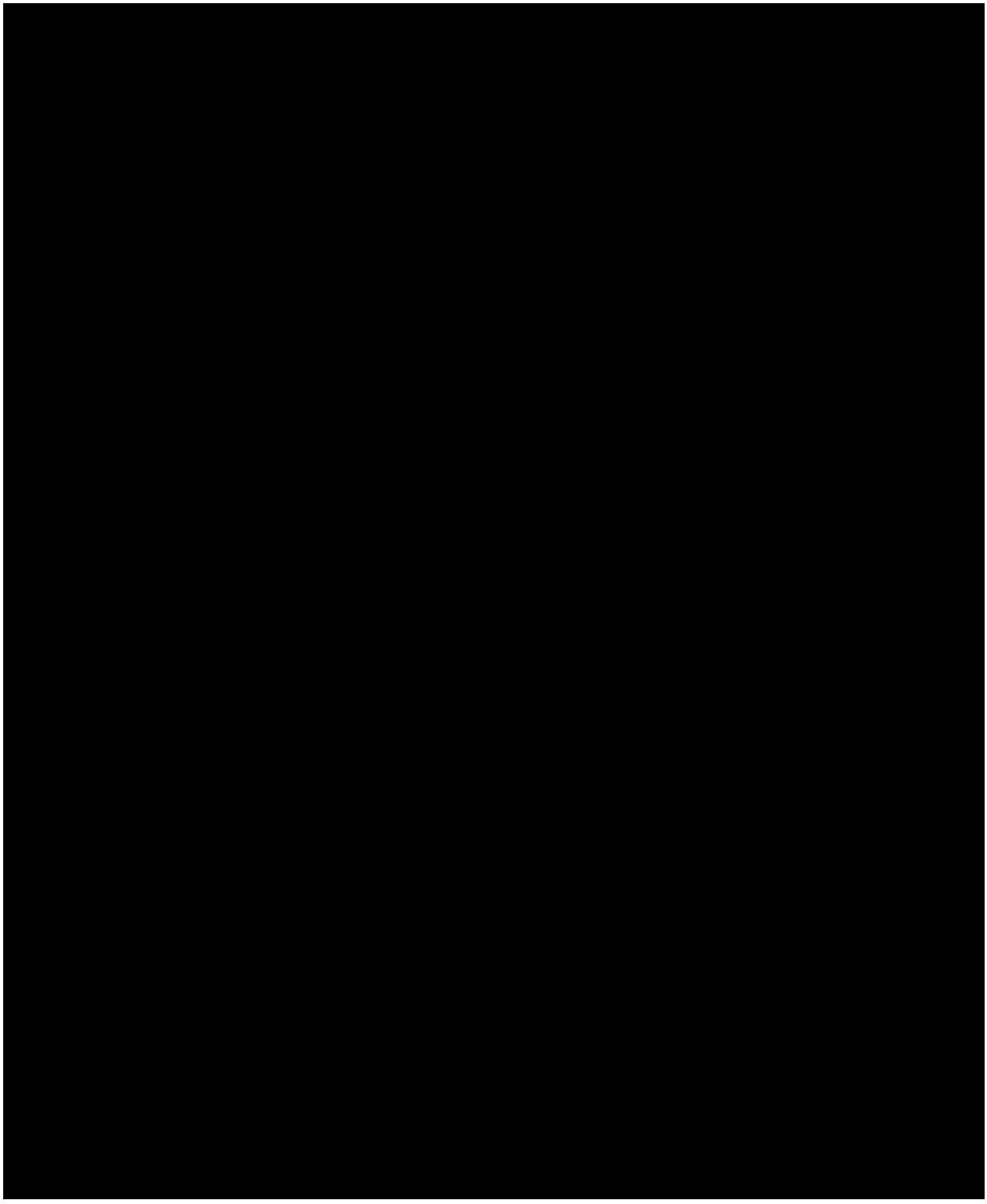

16.3 Appendix 3: Drugs that are prohibited or to be used with caution

Table 16-11 Capmatinib: drugs to be used with caution during co-administration

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, nintedanib, olodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, proguanil, ranolazine, riociguat, risperidone, ritonavir, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
BCRP substrates	atorvastatin daunorubicin, dolutegravir, doxorubicin, ethinyl estradiol, hematoporphyrin, imatinib, irinotecan, methotrexate, paritaprevir, pitavastatin, rosuvastatin, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitor	Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
H_2-receptor antagonists	cimetidine, famotidine, nizatidine, ranitidine
Antacids	aluminum carbonate, aluminum hydroxide, calcium carbonate, calcium hydroxide, bismuth subsalicylate
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (https://drug-interactions.medicine.iu.edu/Main-Table.aspx), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies". NTI: narrow therapeutic index	

Table 16-12 Capmatinib: prohibited drugs

Mechanism of Interaction	Drug Name
Strong CYP3A4 inducer	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (*Hypericum perforatum*)
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (https://drug-interactions.medicine.iu.edu/Main-Table.aspx), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies"	

16.4 Appendix 4: Cockcroft-Gault formula for GRF estimate

Creatinine clearance will be calculated using the following formulas:

Male GFR = (140 - age) x (weight) / (sCr x 72)

Female GFR = (140 - age) x (weight) x 0.85 / (sCr x 72)

GFR is Glomerular Filtration Rate in ml/min; Age is in years; Weight is Lean Body Mass in kilograms; sCr: is Serum Creatinine in mg/dl.

The formulas above should be altered in the following cases:

- Overweight (GFR >25 kg/m2): Calculate based on adjusted body weight;

  Adjusted body weight = wtKgIdeal + 0.4 * (wtKgActual - wtKgIdeal)
- Underweight: Use actual weight, Do not round up to Serum Creatinine (significantly underestimates GFR)
- Elderly: do not round up to Serum Creatinine (significantly underestimates GFR)
- Patients who had a limb amputation: measure 24 hour Creatinine Clearance

Approval Signatures

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