

Novartis Research and Development

INC280

Oncology Clinical Trial Protocol
CINC280D2201 / NCT03647488

A phase II, multicenter, randomized, two-arm study of capmatinib (INC280, an oral MET inhibitor) and spartalizumab (PDR001, a PD-1 inhibitor) combination therapy versus docetaxel in pretreated adult patients with EGFR wild-type, ALK rearrangement negative locally advanced/metastatic non-small cell lung cancer.

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List of abbreviations

Ab	Antibody
ACTH	Adrenocorticotrophic hormone
ADA	Anti-drug Antibodies
ADL	Activity daily living
ADR	Adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALP	alkaline phosphatase
alpha-FP	alpha-fetoprotein
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
ANP	Atrial natriuretic peptide
aPTT	Activated Partial Thromboplastin Time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine triphosphate
AUC	Area under curve
BAL	Bronchoalveolar lavage
BID	Twice a day
BIRC	blinded independent review committee
BLQ	Below the limit of quantification
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
BSA	Body Surface Area
BSC	best supportive care
BUN	blood urea nitrogen
BVN	bivariate normal
C	Cycle
CFR	Code of Federal Regulation
CI	Confidence Interval
CK	Creatine kinase
Cmax	The maximum (peak) concentration of drug in plasma
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
COA	Clinical Outcome Assessments
COPD	Chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CR	Complete Response
CRA	Clinical research associate
CRF	Case Report/Record Form (paper or electronic)
CRS	case retrieval strategy
CSF	Colony-stimulating factor
CSR	Clinical study report

CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CV	coefficient of variation
D	Day
D5W	dextrose 5% in water
DBP	Diastolic Blood Pressure
DCR	Disease control rate
DDE	direct data entry
DDI	Drug-drug interaction
DDS	Dose-determining set
DILI	Drug-Induced Liver Injury
DLCO	Diffusing capacity of the lungs for carbon monoxide
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
DOOR	Duration of response
DRID	Dose reference ID
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGFR	epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EM	electromagnetic
EMA	European Medicines Agency
EOT	End of treatment
EPR	early progression rate
ESA	Erythropoiesis agent
EU	European Union
EWOC	Escalation with overdose control
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FISH	Fluorescent in situ hybridization
FPFV	First patient first visit
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GABA	Gamma-Aminobutyric acid
GCN	Gene copy number
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
h	hour
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody

HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B virus DNA
HCC	Hepatocellular carcinoma
hCG	human chorionic gonadotrophin
HCV	Hepatitis C virus
HCV RNA	Hepatitis C virus RNA
Hgb	Hemoglobin
HGF	Hepatocyte growth factor
HIV	human immunodeficiency virus
HR	Hazard ratio
HSV	Herpes simplex virus
i.v.	intravenous
IB	Investigator's brochure
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
[REDACTED]	[REDACTED]
IEC	Independent Ethics Committee
IFN	Interferon
IG	Immunogenicity
IgG4	Immunoglobulin G4
IHC	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL-2	Interleukin
ILD	Interstitial lung disease
INR	International normalized ratio
IO	Immuno-oncology
[REDACTED]	[REDACTED]
IRB	Institutional Review Board
[REDACTED]	[REDACTED]
IRT	Interactive Response Technology
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
ITT	Intent to treat
[REDACTED]	

IUD	Intrauterine device
[REDACTED]	[REDACTED]
IUS	Intrauterine system
JAGS	Just another Gibbs Sampler
LDH	lactate dehydrogenase
LFT	Liver function test
LH	Luteinizing hormone lightheadedness
LLN	lower limit of normal
LLOQ	Lower limit of quantification
LPLV	Last patient last visit
mAb	monoclonal Antibody
MAP	Meta-analytic-predictive
MCMC	Markov chain Monte Carlo
MedDRA	Medical dictionary for regulatory activities
MET	Tyrosine-protein kinase Met
mg	milligram(s)
mL	milliliter(s)
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NaF	Sodium fluoride
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NGS	Next generation sequencing
NL	New lesion
NLNT	New lesion non-target
NLT	New lesions target
[REDACTED]	[REDACTED]
NSAIDS	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small-cell lung carcinoma
NTL	Non-target lesion
ORR	Objective response rate
OS	Overall survival
PAS	Pharmacokinetic analysis set
PCR	Polymerase chain reaction
PD	pharmacodynamic(s)
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PK	pharmacokinetic(s)

PLT	Platelet
PPI	Proton-pump inhibitor
PR	Partial response
PS	Performance status
QD	Daily
QMS	Quality management system
QTcF	Fridericia QT correction formula
QxW	Every x week(s)
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RoW	Rest of the World
RP2D	Recommended Phase 2 dose regimen
RT-PCR	Reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	The Statistical Analysis Plan (SAP) is a regulatory document which provides evidence of preplanned analyses
SBP	Systolic blood pressure
SD	standard deviation
SD	Stable Disease
SOD	Sum of Diameter
SOP	Standard operating procedure
SUSARs	Suspected unexpected serious adverse reactions
TBIL	Total bilirubin
TdP	Torsades de Pointes
TFQ	Trial feedback questionnaire
TKI	Tyrosine kinase inhibitor
TL	Target lesion
TNBC	Triple negative breast cancer
TP	Time point
TSH	Thyroid-stimulating hormone
TTF	Time to treatment failure
TTP	Time to progression
TTR	Time to response
UC	Unchanged
ULN	upper limit of normal
UNK	Unknown
US	United States, ultrasound
VAS	Visual analogue scale
VATS	Video-assisted thoracic surgery
WHO	World Health Organization
wt	wild type

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
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)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance"
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
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. Withdrawal of study consent: 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
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Study treatment interruption	Includes any delay or withholding of study treatment for any reason as well as an interruption during an infusion of study treatment for any reason
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, <u>and</u> does not want any further visits or assessments, <u>and</u> does not want any further study related contact, <u>and</u> does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CINC280D2201
Full Title	A phase II, multicenter, randomized, two-arm study of capmatinib (INC280, an oral MET inhibitor) and spartalizumab (PDR001, a PD-1 inhibitor) combination therapy versus docetaxel in pretreated adult patients with EGFR wild-type, ALK rearrangement negative locally advanced/metastatic non-small cell lung cancer.
Brief title	Study of efficacy and safety capmatinib (INC280, an oral MET inhibitor) and spartalizumab (PDR001, a PD-1 inhibitor) combination therapy versus docetaxel in pretreated adult patients with locally advanced/metastatic non-small cell lung cancer
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	<p>The purpose of this prospective, multicenter, randomized phase II study is to evaluate the safety and efficacy of the combination of capmatinib and spartalizumab in subjects with EGFR wt (for exon 19 deletions and exon 21 L858R substitution mutations), ALK-negative rearrangement, advanced/metastatic (stage IIIB (not amenable for definitive chemo-radiotherapy) or IV) NSCLC, regardless of MET and PD-L1 status</p> <p>The study will enroll subjects with advanced/metastatic NSCLC which are EGFR wt, ALK negative, after failure of prior platinum doublet and checkpoint inhibitor administered for the treatment of the advanced stage disease. Subjects must be docetaxel naive. A Run-in part will be conducted to determine safety, tolerability and preliminary efficacy of the capmatinib and spartalizumab combination. A Randomized part will be conducted to assess the overall survival (OS) of the combination of capmatinib and spartalizumab in comparison to docetaxel.</p>
Primary Objective(s)	<p>Part 1: Run-in</p> <ul style="list-style-type: none"> • To assess the safety and tolerability of the capmatinib and spartalizumab combination. <p>Part 2: Randomized</p> <ul style="list-style-type: none"> • To assess the overall survival of the combination of capmatinib and spartalizumab in comparison to docetaxel.
Secondary Objectives	Part 2 Randomized part: To assess objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DOR) and time to response (TTR) based on RECIST 1.1 (Response Evaluation Criteria in Solid Tumors). To assess the incidence and severity of adverse events (AEs) and serious adverse events (SAEs).
Study design	<p>This is a two-part prospectively designed, multicenter, open-label, randomized phase II study to evaluate the safety and the efficacy of capmatinib in combination with spartalizumab in adult subjects with EGFR wild type and ALK rearrangement negative advanced stage IIIB or IV NSCLC after failure of platinum doublet chemotherapy and checkpoint inhibitor treatment.</p> <p>Part 1: run-in phase: will confirm the safety and tolerability and assess the efficacy of the combination of capmatinib and spartalizumab.</p> <p>Part 2: randomized phase: will evaluate the efficacy and safety of the combination of capmatinib and spartalizumab compared to docetaxel</p>
Population	The study population (15 subjects in run-in phase and 90 subjects in randomized phase, total of 105 subjects) will include adult subjects with locally advanced stage IIIB/IV non-small cell lung cancer. Subjects will be docetaxel naive, and subjects with EGFR mutations and ALK rearrangements will be excluded.

Key Inclusion criteria	<ul style="list-style-type: none"> • Histologically confirmed locally advanced/metastatic (stage IIIB/IV) per AJCC/IASLC v.8) • EGFR wild-type, ALK rearrangement negative, NSCLC • Subject has demonstrated progression following one prior platinum doublet and one prior PD-(L)1 checkpoint inhibitor (either alone or in combination, the most recent treatment regimen must have contained a PD-(L)1 checkpoint inhibitor) • Subjects must be candidates for single agent docetaxel • Subjects must have at least one lesion evaluable by RECIST 1.1
Key Exclusion criteria	<ul style="list-style-type: none"> • Prior treatment with a MET inhibitor or HGF (Hepatocyte growth factor) targeting therapy • Any untreated central nervous system (CNS) lesion • Use of any live vaccines against infectious diseases within 12 weeks of initiation of study treatment.
Study treatment	Capmatinib and spartalizumab combination or docetaxel
Efficacy assessments	<ul style="list-style-type: none"> • Survival assessment • Tumor response assessed locally per RECIST 1.1
Key safety assessments	<ul style="list-style-type: none"> • Physical examinations • Eastern Cooperative Oncology Group performance status (ECOG PS) • Monitoring of laboratory assessments in blood and urine • Adverse event monitoring • Electrocardiograms • Monthly urine pregnancy tests
Other assessments	<p>[REDACTED]</p> <ul style="list-style-type: none"> • Pharmacokinetics (PK)/ immunogenicity (IG) samples <p>[REDACTED]</p>
Data analysis	<p>All analysis sets are defined in Section 12.1.</p> <p>In the run-in part safety and tolerability data will be assessed when all patients in this phase have at least 24 weeks of follow-up as well as preliminary efficacy.</p> <p>In the randomized part, the primary analysis will be performed when approximately 60 overall survival events have been observed. Overall Survival (OS) is defined as the time from the date of randomization/start of treatment to date of death due to any cause. A cut-off date will be established for analysis of OS. All deaths occurring on or before the cut-off date in the Full Analysis Set (FAS) will be used in the OS analysis. If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact. The analysis of OS will be based on full analysis set which includes who received at least one dose of any component of study treatment and all randomized subjects. The estimated hazard ratio (HR) between capmatinib and spartalizumab combination and docetaxel and exact 80% confidence interval will be assessed.</p> <p>The expected median OS for docetaxel as second-line chemotherapy is ~8 months (Herbst et al 2016, Rittmeyer et al 2017). A 33.3% reduction in hazard rate for overall survival in capmatinib plus spartalizumab arm compared to docetaxel arm will correspond to an increase in median OS by 4 months under the exponential assumption.</p> <p>Considering a 2:1 randomization, with approximately 60 OS events, the probability of observing clinically relevant activity is 66% when the true HR is 0.60 and the probability of observing clinically relevant activity is 24% when the true HR is 0.80. The secondary efficacy endpoints, objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), time to response (TTR), duration of response (DOR) and disease control rate (DCR) based on the investigator assessed as per RECIST 1.1 will be analyzed. ORR and DCR will be summarized with accompanying 95% confidence interval (CI). PFS, TTR, DOR and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented.</p>
Key words	INC280, PDR001, capmatinib, spartalizumab, docetaxel, NSCLC, EGFR wt, ALK rearrangement negative, MET inhibitor

1 Introduction

1.1 Background

Lung cancer has been the most common cancer in the world for several decades. In 2012, there were an estimated 1.8 million new cases, representing 12.9% of all new cancers worldwide. It was also the most common cause of death from cancer, with 1.6 million deaths representing 19.4% of the total deaths from cancer ([Ferlay et al 2015](#)). For 2017, approximately 155,870 deaths due to lung cancer are expected in the United States (US) ([Siegel et al 2017](#)) and 275,700 deaths are predicted in the European Union ([Malvezzi et al 2017](#)).

The World Health Organization (WHO) divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC accounts for more than 85% of all lung cancer cases, and it includes 2 major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types); and (2) squamous cell (epidermoid) carcinoma. Adenocarcinoma (40% of lung cancers; 47% in NSCLC) is the most common type of lung cancer seen in the United States and is also the most frequently occurring cell type in nonsmokers ([Novello et al 2016](#)). One reason for the high mortality rate of lung cancer is the advanced stage at diagnosis; only 25 to 30% of new NSCLC cases are diagnosed with localized disease that is potentially curable with surgery ([Nguyen et al 2012](#)). The majority of subjects are diagnosed with locally advanced or metastatic disease and they are not candidates for surgery.

Platinum combination therapy is superior to best supportive care in subjects with advanced, incurable disease, and platinum doublet chemotherapy (i.e., cisplatin or carboplatin in combination with other chemotherapy agents, with or without bevacizumab) has been the standard initial (i.e., first-line) treatment for subjects with locally advanced or metastatic (i.e., stage IIIB or IV) NSCLC in absence of a druggable molecular driver or PD-L1 (Programmed Death-Ligand 1) expression >1% ([Novello et al 2016](#), [NCCN 2018](#)). Pemetrexed-based platinum doublet therapy has become a standard first-line treatment option for NSCLC subjects with non-squamous histology. In a Phase 3, non-inferiority trial of chemotherapy-naive subjects with stage IIIB or IV NSCLC, pemetrexed plus cisplatin (pemetrexed/cisplatin) was shown to be non-inferior to (median OS 10.3 versus 10.3 months, respectively) and better tolerated than gemcitabine/cisplatin ([Scagliotti et al 2008](#)). With respect to OS, pemetrexed/cisplatin was superior to gemcitabine/cisplatin in the subset of subjects with adenocarcinoma (OS 12.6 versus 10.9 months, respectively) and large-cell carcinoma (10.4 versus 6.7 months, respectively).

Single agent chemotherapy like pemetrexed (in non-squamous) or docetaxel (in any histology) are established treatment options for pretreated NSCLC subjects and have served as the control arms of several prospective, randomized trials in second or third setting. In a randomized trial comparing both agents in the second-line setting, efficacy was similar with both treatments (the response rate of approximately 9-10%, median PFS of 2-3 months, and median OS of approximately 7-8 months), although pemetrexed was associated with less toxicity ([Hanna et al 2004](#)). Overall, the reported response rates to second-line chemotherapy also with other single agent chemotherapeutics have generally been < 11% with median PFS and OS generally below 4 and 11 months respectively ([de Marinis and Grossi 2008](#), [Weiss and Stinchcombe 2013](#), [Novello et al 2016](#), [NCCN 2018](#)). Upon progression after second-line chemotherapy, subjects may be candidates for further treatment, although

randomized evidence is scarce and most data come from phase II trials or retrospective analyses. Subjects have often limited response to third line therapy, although it may have a useful palliative effect ([Shepherd et al 2005](#), [de Marinis and Grossi 2008](#), [Eccles et al 2011](#), [Reck et al 2014](#), [Besse et al 2014](#), [NCCN 2018](#)).

Activating mutations in EGFR and ALK translocations have been the first molecular drivers to show strong predictive value of improved efficacy and better tolerance of EGFR and ALK Tyrosine Kinase Inhibitors (TKIs) when compared with standard chemotherapy in subjects harboring EGFR activating mutations and ALK translocations, becoming the new standard of care in both the pretreated setting and in treatment naive setting ([Ettinger et al 2010](#), [Sequist et al 2013](#), [Zhou et al 2011](#), [Fukuoka et al 2011](#), [Shaw and Engelman 2013](#), [Shaw et al 2013](#), [Rosell et al 2012](#), [Solomon et al 2014](#), [NCCN 2018](#)). Importantly, due to the high oncogenic addiction to the molecular abnormality during the course of the disease, the efficacy of these targeted therapies seem to be independent of line of treatment, and high response rates are still observed in subjects who received several treatments (generally excluding therapies targeting the same pathway) before receiving the given targeted therapy ([Camidge et al 2012](#)). The success of EGFR and ALK TKIs highlights the importance of identifying specific molecular drivers of NSCLC to appropriately direct targeted agents in specific subject populations. Similarly, other TKIs targeting rarer targets like ROS1 translocation and BRAF mutation are now available in these subject subsets ([Solomon et al 2014](#), [Hamanishi et al 2016](#)). The potential for prolonged response by targeting these oncogenic drivers delays the need for chemotherapy or other treatments. The landscape of NSCLC treatment is changing and the treatment paradigm of “one size fits all” has progressively switched to a personalized therapy.

Monoclonal antibody (mAb) inhibitors of immunological checkpoints, including PD-1 and PD-L1, have demonstrated significant antitumor activity in subjects with various solid tumors with less toxicity than chemotherapy or broad immune activators, such as IL-2 (interleukin-2) and IFN- α (interferon- α). PD-1 is a particularly important immunological target, with inhibitors active across a variety of solid tumors. Two mAbs targeting PD-1, pembrolizumab and nivolumab, have demonstrated significant single agent activity in melanoma, NSCLC and other solid tumors ([Hamanishi et al 2016](#)).

Inhibitors of programmed death 1 (PD-1) and its ligand PD-L1 are effective therapies for metastatic NSCLC lacking sensitizing EGFR or ALK mutations. PD-(L)1 inhibitors (nivolumab, pembrolizumab, atezolizumab) are now standard of care in second/third-line NSCLC; pembrolizumab is also approved in first-line (PD-L1 $\geq 50\%$) and in combination with platinum chemotherapy (irrespective of PD-L1 status). Results of several studies with immunotherapy/platinum chemotherapy and immunotherapy plus immunotherapy (ipilimumab/nivolumab, tremelimumab/durvalumab) are becoming available in 2018/19 which might further reshape the treatment landscape in first-line, shifting treatment paradigms in later lines of treatment ([Gandhi et al 2018](#)).

Checkpoint inhibitors are currently being evaluated in additional phase III studies with immunotherapy-based treatment in both pretreated and first-line setting, with several regulatory approvals expected in 2018 and 2019.

Overall, currently approved PD-1 (nivolumab and pembrolizumab) and PD-L1 (atezolizumab) inhibitors have shown ORR 17-19%, median PFS 2-4 months, and overall survival of 9-14

months, in subjects who progressed after first line platinum doublet in randomized phase 3 studies versus docetaxel (Herbst et al 2016, Rittmeyer et al 2017, Borghaei et al 2015).

With the advancement of immunotherapy in the treatment of NSCLC, more and more subjects are exposed to checkpoint inhibitors in the course of their disease, either as single agents or in combination with other anticancer therapies. As disease progression is inevitable in these subjects, the need to develop innovative therapies which are effective in this post-immunotherapy, second, and third-line setting is currently critically important. The efficacy of standard therapies, including docetaxel or rechallenging with immunotherapy-based therapies after progression on checkpoint inhibitors, is currently unknown (UNK) with only anecdotal reports (Park and Cheung 2017, Schvartsman et al 2017).

1.1.1 MET and capmatinib (INC280)

In human malignant disease, the MET pathway is frequently dysregulated, triggering a diverse set of signaling cascades (including the RAS-MAPK as well as the PI3K-AKT pathway), which are promoting proliferation, survival, motility and angiogenesis (Christensen et al 2005). In addition, various roles of MET/HGF signaling in immune cells, primarily of the myeloid lineage, have been proposed that could lead to MET-dependent immune suppression (Molnarfi et al 2015). Several mechanisms have been identified by which the MET pathway becomes aberrantly activated in cancer such as gene amplification, receptor overexpression, mutations, autocrine or paracrine secretion of its ligand HGF. MET amplification and MET mutations are currently the most studied MET dysregulations in NSCLC, being evaluated as predictors of response to MET inhibitors. Overall MET dysregulation is rare.

MET amplification (with gene copy number [GCN] > 6) is reported in ~3-4% of NSCLC (Comprehensive molecular profiling of lung adenocarcinoma, 2014) with up to 1% of these tumors demonstrating even higher levels of amplification (GCN ≥ 10). Responses to MET inhibitors in NSCLC harboring high levels of MET amplification have been reported in clinical trials (Schuler et al 2016, Wolf 2017, Camidge et al 2018).

MET mutations causing skipping of exon 14, thereby removing the juxtamembrane domain of MET, leads to protein stabilization and oncogenic activation (Kong-Beltran et al 2006). Next generation sequencing of tumor specimens identified many different variants that can result in exon 14 skipping. These variants are primarily found in lung cancer at a frequency of about 3% (Frampton et al 2015, Schrock et al 2016). Recent clinical observations indicate that such mutations are predictors of response to capmatinib and other MET targeting agents (Frampton et al 2015, Paik et al 2015, Jenkins et al 2015, Mendenhall and Goldman 2015, Waqar et al 2015, Liu et al 2015, Schuler et al 2016, Drilon 2016, Cedrés et al 2018).

Numerous effects of MET signaling on immune cells have been reported in the preclinical literature (Molnarfi et al 2015). For example, activation of MET through HGF was found to impact 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.

Recent studies in multiple mouse models have demonstrated that MET-positive neutrophils suppress immune therapy-induced T cell expansion and effector functions, and that concomitant MET inhibition with capmatinib can enhance the efficacy of cancer immunotherapies in non-

MET driven tumor models ([Glodde et al 2017](#)). It has also been reported that MET is expressed on a subset of cytotoxic T lymphocytes suppressing their function when activated by HGF. These observations demonstrate an immunomodulatory potential of MET and HGF by directly acting on immune cells, irrespective of the MET dysregulation. MET inhibitors also may restore immune cell function by preventing/reducing hepatocyte growth factor (HGF) signaling. Additional information supporting the role of MET inhibitors like capmatinib as immunomodulators can be found in [Section 4.2.1](#).

MET dysregulation is a negative prognostic factor in patients with NSCLC ([Guo et al 2014](#), [Landi et al 2017](#), [Awad et al 2017](#)), particularly when both MET amplification and mutation occur in the same tumor ([Awad et al 2017](#)).

While no selective MET inhibitors or antagonists have been approved for use in cancer patients to date, several investigational agents are being currently evaluated in clinical trials.

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](#)) capable of blocking MET activation developed primarily in MET dysregulated solid tumors. Capmatinib also exhibits preclinical immunomodulatory activity in tumor models irrespective of MET dysregulation.

Overall, preclinical and early clinical data indicate that capmatinib has a manageable safety profile. As of the cut-off date of 28-Sep-2017, a total of 1109 cancer subjects and 158 non-cancer subjects have received capmatinib. A total of 622 subjects with solid tumors have been treated with capmatinib as a single agent, and 487 subjects have been treated with capmatinib in combination therapies. Treatment was with either the capsule formulation or tablets or both. Twenty-one clinical studies are currently ongoing with capmatinib. A total of 19 subjects have experienced 25 Dose Limiting Toxicities (DLTs): 6 subjects in single agent studies and 13 in combination studies. For more information, please refer to the current [capmatinib Investigator's Brochure (IB)].

Overall, the majority of the reported adverse events (AEs) are mild or moderate in severity. The most frequent AEs suspected to be related to capmatinib of any grade reported in the largest single agent trial [CINC280A2201] (220 subjects) were edema peripheral (77 subjects, [35.0%]), nausea (69 subjects, [31.4%]), vomiting (40 subjects, [18.2%]), blood creatinine increased (39 subjects, [17.7%]), and fatigue (34 subjects, [15.5%]), majority Grade 1/2. The most frequently occurring Grade 3/4 AEs suspected to be related to capmatinib as a single agent included edema peripheral and lipase increased (each in 9 subjects, [4.1%]), fatigue (8 subjects, [3.6%]), alanine aminotransferase increased (ALT) (7 subjects, [3.2%]), aspartate aminotransferase increased (AST), hypophosphataemia, nausea and vomiting (each in 3 subjects, [1.4%]).

Caution is recommended when capmatinib is administered in combination with other anticancer drugs with a known risk of hepatotoxicity. One case of liver function test (LFT) abnormal meeting Hy's Law criteria for hepatotoxicity (PHHO2015CN003025) has been reported for a subject enrolled in the NSCLC combination study with gefitinib [CINC280X2202]. The event could not be attributed solely to either drug alone or to the combination. The subject permanently discontinued both study drugs. Liver function tests improved after treatment discontinuation.

As of the IB cut-off of 28-Sep-2017, pneumonitis and ILD (interstitial lung disease) have been reported from both capmatinib single agent and combination studies with the 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.

The maximum tolerated dose (MTD) for capmatinib capsules or tablets as single agent was not reached. The RP2D (Recommended Phase 2 dose regimen) for capmatinib as a single agent has been determined to be 600 mg BID (twice a day) in capsule formulation and 400 mg BID in tablet formulation. For more information, please refer to the current [capmatinib Investigator's Brochure].

1.1.2 Spatalizumab (PDR001)

Spatializumab (PDR001) is a monoclonal antibody (mAb) directed against human Programmed Death-1 (PD-1). PD-1 is a critical immune-checkpoint receptor that is expressed on CD4 and CD8 T cells upon activation ([Freeman and Sehn 2018](#)). Engagement of PD-1 by its ligands, PD-L1 and PD-L2 (Programmed Death-Ligand 2), transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function ([Riley et al 2009](#)). During tumorigenesis, cancer cells from a wide range of tumor types exploit immune checkpoint pathways, such as PD-L1, to avoid detection by the adaptive immune system ([Murphy et al 2011](#)). Monoclonal antibody (mAb) inhibitors of immunological checkpoints, including PD-1 and PD-L1 mAb's, have demonstrated significant antitumor activity in patients with various solid tumors.

Spatializumab 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. Anti-drug antibodies (ADA) to spatalizumab were observed in some spatalizumab treated cynomolgus monkeys. A trend of reduced drug exposure was observed in these ADA-positive animals. For further details, please refer to the latest [spatalizumab Investigator's Brochure].

As of 19-Jan-2018 (latest IB cut-off date), approximately 1239 subjects across 23 Novartis-sponsored clinical studies have been treated with spatalizumab. Of these, a total of 517 subjects were exposed to spatalizumab single agent, and 722 subjects were exposed to spatalizumab in combination with other agents (LBH589, LCL161, CJM112, EGF816, ACZ885 and TMT212, LAG525, MBG453; other combination studies with spatalizumab have not yet gathered sufficient PK data to warrant inclusion in the IB).

The available safety data from these clinical studies indicate that spatalizumab is generally well tolerated. In the dose escalation phase of the first-in-man study CPDR001X2101 in patients with advanced solid tumors, no DLTs were reported. The preliminarily identified safety risks associated with spatalizumab 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.

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 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.

Adverse events of special interest (AESI) for spartalizumab include endocrinopathies, colitis, skin reactions, hepatitis, nephritis, pneumonitis and other irAEs, and infusion reactions.

Based on the available pharmacokinetics (PK) and safety data, two RP2Ds for spartalizumab have been declared: 400 mg Q4W or 300 mg Q3W, with the choice between these two regimens determined by scheduling convenience, for example in combination settings. The safety profile was similar across the different dose and disease groups and is consistent with the safety profile of other similar PD-1 inhibitors.

For further details, please refer to the latest version of the [spartalizumab Investigator's Brochure], as well as [Section 4.5](#) (Risks and Benefits) and [Section 6.5.3.1](#) (Dose Modifications) of the protocol.

1.1.3 Combination of capmatinib with a checkpoint inhibitor

1.1.3.1 Combination of capmatinib and nivolumab

The combination of capmatinib and nivolumab has been explored in the study [CEGF816X2201C]. This is an ongoing phase II, open-label, study of capmatinib in combination with nivolumab in adult subjects with advanced immunotherapy immunotherapy (IO)-naive NSCLC (either with high or low MET expression). As of the data cutoff of 10-Aug-2017, 18 subjects have been enrolled and treated with capmatinib 400 mg BID + nivolumab 3 mg/kg Q2W.

All 18 subjects (100%) experienced AEs of any grade, regardless of causality. The most common AEs (occurring in more than 20% of subjects) of any grade were nausea (77.8%), vomiting (61.1%), diarrhea (44.4%), rash (group term that includes rash, macular rash, maculopapular rash, and eczema, 44.4%), constipation (33.3%), peripheral edema (33.3%), decreased appetite (27.8%), fatigue (27.8%), pyrexia (27.8%), increased amylase (22.2%),

arthralgia (22.2%), asthenia (22.2%), back pain (22.2%), and dyspnoea (22.2%); the majority of AEs were Grade 1/2.

With regard to AEs suspected to be related to study treatment, all 18 subjects (100%) experienced AEs of any grade. The most frequent AEs (occurring in more than 10% of subjects) of any grade suspected to be related to study treatment were nausea (77.8%), diarrhea (44.4%), rash (group term, 44.4%), vomiting (44.4%), peripheral edema (33.3%); decreased appetite (27.8%), increased amylase (22.2%), asthenia (22.2%), fatigue (22.2%), arthralgia (22.2%), increased blood creatinine (16.7%), hypoalbuminemia (16.7%), lethargy (16.7%), neutropenia (16.7%), pyrexia (16.7%), constipation (11.1%), dry skin (11.1%), increased lipase (11.1%), pruritus (11.1%), and thrombocytopenia (11.1%); the majority of AEs were Grade 1/2.

Ten subjects (55.6%) experienced at least one SAE regardless of causality. Five subjects (27.8%) experienced at least one SAE suspected to be related to study treatment. These included SAEs of lethargy, gastroesophageal reflux disease, somnolence, and temporal arteritis in one subject; pyrexia in one subject; pyrexia, maculopapular rash, neutropenia, thrombocytopenia, and disseminated intravascular coagulation in one subject; anaphylactic reaction in one subject; macular rash and vomiting in one subject; and colitis, vomiting, and diarrhea in one subject. Each of these suspected related SAEs were reported as recovered, except for temporal arteritis (recovering) and colitis (not recovered).

Overall, the safety profile of this combination was manageable; however, the data generated in this study are still preliminary, and caution is warranted due to the partial overlapping toxicity from both single agents.

This study has provided initial information regarding the safety of the combination of a PD-1 inhibitor and capmatinib; efficacy data generated in this setting of pretreated advanced NSCLC subjects will further support the rationale for combining capmatinib with spartalizumab in advanced NSCLC in this CINC280D2201 study.

1.1.3.2 Combination of capmatinib and spartalizumab

Capmatinib in combination with spartalizumab is currently being evaluated in the dose escalation and expansion study [CINC280X2108] in subjects with hepatocellular carcinoma (HCC).

This is an ongoing phase Ib/II, open-label, multi-center study of capmatinib in combination with spartalizumab or spartalizumab single agent conducted in advanced IO-naive hepatocellular carcinoma after sorafenib failure.

As of the data cut-off of 25-Sep-2017 [capmatinib Investigator's Brochure], 20 subjects were enrolled and treated in the dose escalation (phase Ib) part of the study, at three dose levels: 200 mg BID capmatinib (N=6), 300 mg BID capmatinib (N=8) and 400 mg BID capmatinib (N=6), all in combination with 300 mg Q3W spartalizumab.

One DLT was reported for a subject treated with capmatinib 400 mg (BID) in combination with spartalizumab 300 mg (Q3W): Grade 3 diarrhea, suspected to be related to study treatment. Seven subjects (35%) have permanently discontinued study treatment, 1 subject (5%) due to an AE, 4 subjects (20%) due to progression of disease, 1 subject (5%) due to subject/guardian decision and 1 subject (5%) due to death (caused by progression of disease).

AEs, all grades, regardless of relationship to study drug, were reported in 19 subjects (95%) overall, with the most frequent AEs being peripheral edema (10 subjects, 50%), nausea (7 subjects, 35%), blood creatinine increased, fatigue (each in 6 subjects, 30%), and rash (5 subjects, 25%).

Of the 20 subjects treated, 9 (45%) experienced Grade 3 or Grade 4 AEs regardless of relationship to study drug. The most frequent Grade 3/4 AEs included nausea, dyspnoea, ALT increased, bilirubin increased (each in 2 subjects, 10%). Seven subjects (35%) had Grade 3/4 AEs suspected to be related to study treatment: nausea (2 subjects, 10%), peripheral edema, ALT increased, diarrhea, stomatitis, hypotension, platelet count decreased, acute myocardial infarction, unstable angina, blood bilirubin increased, dehydration and neutropenia (each in 1 subject, 5%).

Of the 20 subjects treated, 17 (85%) experienced AEs (all grades) suspected to be related to study treatment. The most frequent suspected AEs included peripheral edema (9 subjects, 45%), fatigue, rash (each in 5 subjects, 25%), blood creatinine increased, nausea, vomiting (each in 4 subjects, 20%).

SAEs, all grades, regardless of relationship to study drug, were reported in 4 subjects (20%). 50% of the SAEs were Grade 3 or 4 (3 out of 6). SAEs suspected to be related to study treatment included unstable angina pectoris, dehydration and diarrhea.

Similar to the combination with nivolumab described in [Section 1.1.3.1](#), the safety profile of the combination of capmatinib and spartalizumab was manageable. The RP2D of the combination of capmatinib and spartalizumab has been established at a dose of capmatinib 400 mg BID and spartalizumab 300 mg Q3W. At this dose level the combination was well tolerated and there was one DLT, Grade 3 diarrhea, as outlined above. While the safety findings generated in this study might be extrapolated to other disease settings, it should be noted that HCC subjects tend to represent a unique subject population, prone to exacerbated toxicity due to their underlying disease and related comorbidities. Further monitoring and confirmation of the safety of this drug combination in this NSCLC indication will be conducted in this CINC280D2201 study, which will use a different schedule for spartalizumab (400 mg Q4W).

1.2 Purpose

The purpose of this prospective, multicenter, randomized phase II study is to evaluate the safety and efficacy of the combination of capmatinib and spartalizumab in subjects with EGFR wt (for exon 19 deletions and exon 21 L858R substitution mutations), ALK-negative rearrangement, advanced/metastatic (stage IIIB [not amenable for definitive chemo-radiotherapy] or IV) NSCLC, regardless of MET and PD-L1 status. Subjects must have progressed on prior treatment with a platinum doublet and a checkpoint inhibitor (either approved or investigational), either as single treatments or in combination. A run-in phase will be conducted before starting the randomized phase to evaluate safety, tolerability and preliminary efficacy of the combination of capmatinib 400 mg BID and spartalizumab 400 mg i.v. Q4W in the selected NSCLC setting.

This study will generate clinical data with the proposed combination doses/schedule for capmatinib and spartalizumab in advanced NSCLC. Additionally, this study will be the first to evaluate the activity of capmatinib in combination with a checkpoint inhibitor in NSCLC in a

post-checkpoint and post-platinum setting and will also confirm the efficacy of docetaxel in this setting.

2 Objectives and endpoints

Objectives and related endpoints are described in [Table 2-1](#) below.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s) <ul style="list-style-type: none">Run-in part: To assess safety and tolerability of capmatinib and spartalizumab combinationRandomized part: To assess the overall survival of combination of capmatinib and spartalizumab in comparison to docetaxel	Endpoint(s) for primary objective(s) <ul style="list-style-type: none">Run-in part: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs, dose interruptions, reductions, and dose intensity.Randomized part: Overall Survival
Secondary objective(s) <ul style="list-style-type: none">To assess the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DOR), and time to response (TTR) of the capmatinib and spartalizumab combination and that of docetaxelTo assess the safety profile of capmatinib and spartalizumab combination therapyTo characterize the pharmacokinetics of capmatinib and spartalizumab as a combination therapy in this patient populationTo evaluate the prevalence and incidence of immunogenicity	Endpoint(s) for secondary objective(s) <ul style="list-style-type: none">Objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DOR), and time to response (TTR) based on RECIST 1.1Incidence and severity of AEs and SAEsPharmacokinetic parameters (e.g. C_{trough}, C_{max}, AUC)Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on treatment

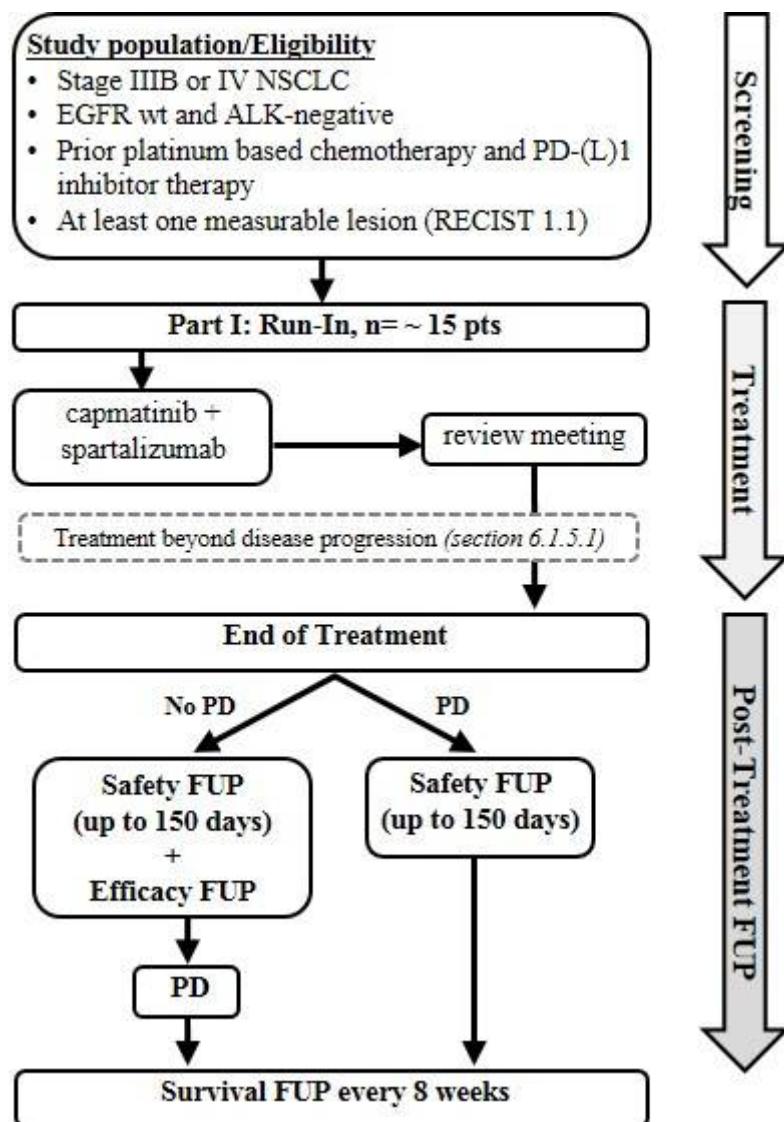
3 Study design

This is a two-part prospectively designed, multicenter, open-label, randomized phase II study to evaluate the safety and efficacy of capmatinib in combination with spartalizumab in adult subjects with EGFR wt (for exon 19 deletions and exon 21 L858R substitution mutations), ALK rearrangement negative in locally advanced (stage IIIB, not eligible for definitive chemo-radiation) or metastatic (stage IV) NSCLC after failure of platinum doublet and checkpoint inhibitor treatment. The study will enroll approximately 105 subjects (approximately 15 subjects in the run-in [part 1] and 90 subjects in the randomized phase [part 2]). Crossover is not allowed.

Part 1: Run-in

Prior to the randomized part of the study, a run-in to assess the safety and tolerability as well as preliminary efficacy of the capmatinib and spartalizumab combination will be conducted. Approximately 15 subjects will be enrolled and treated with capmatinib and spartalizumab combination. A review meeting will take place after all subjects have at least 24 weeks of follow-up. The decision to expand the study to the randomized part will be based on the safety, tolerability, and preliminary efficacy of the capmatinib and spartalizumab combination.

Refer to [Figure 3-1](#) for an overview of the Part I study design.

Figure 3-1 Study Design Part 1: Run-in

pts: patients FUP: follow-up

Part 2: Randomized

In the randomized part, approximately 90 subjects will be randomized in a 2:1 ratio to either capmatinib plus spartalizumab (n=60) or docetaxel (n=30). Subjects will be stratified based on the number of prior lines of therapy (1 vs. >1). The primary objective of part 2 is to assess the overall survival of the combination of capmatinib with spartalizumab in comparison to docetaxel.

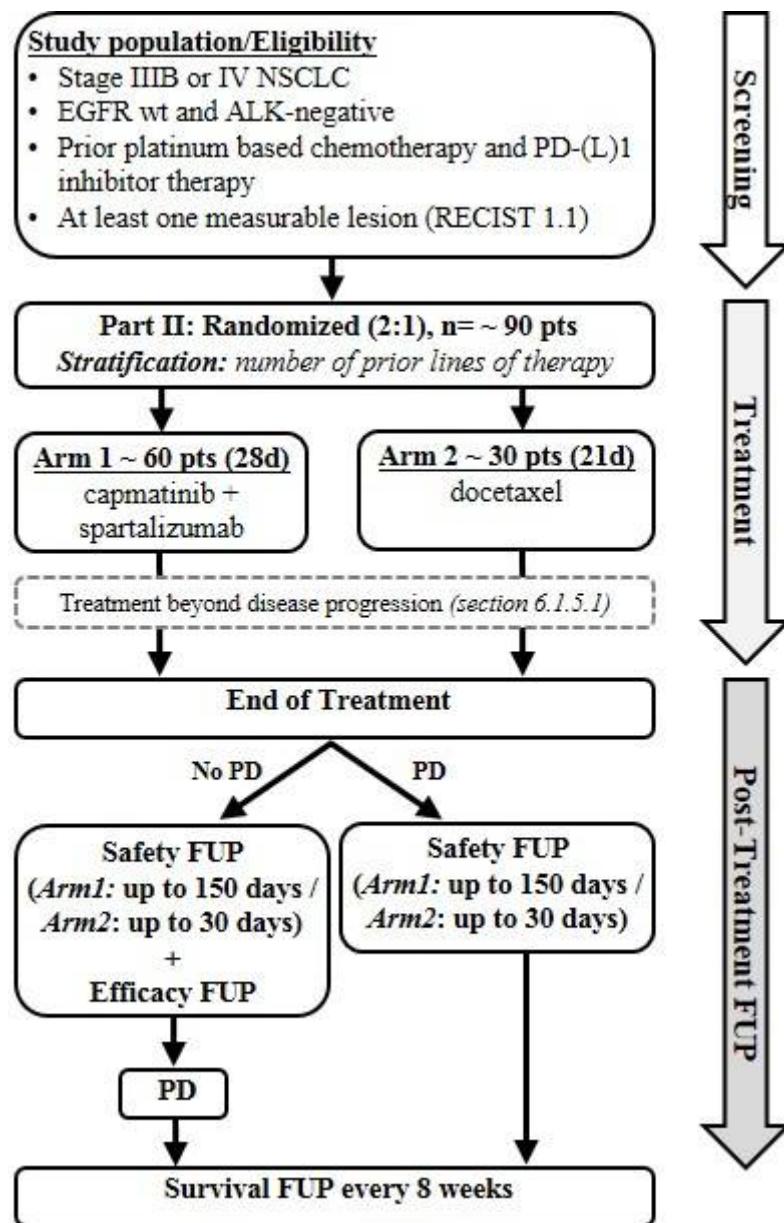
Subjects will continue treatment with capmatinib and spartalizumab combination or docetaxel until they experience any of the following: documented disease progression by RECIST 1.1 (as assessed by the investigator), withdrawal of consent, pregnancy, lost to follow-up, or death irrespective of start of new anti-neoplastic therapy (please refer to [Section 9](#)).

For all subjects (either in the run-in part or randomized to capmatinib and spartalizumab or randomized to docetaxel), the respective treatment (either with capmatinib and spartalizumab combination or docetaxel) may be continued beyond initial disease progression as per RECIST 1.1 (as assessed by the investigator) 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 6.1.5.1](#)).

After treatment discontinuation, all subjects will be followed for safety evaluations during the safety follow-up period, and the subject's status will be collected every 8 weeks as part of the survival follow-up (for additional details please refer to [Section 9](#)).

Refer to [Figure 3-2](#) for an overview of the Part 2 study design.

Figure 3-2 Study Design Part 2: Randomized



pts: patients FUP: follow-up

4 Rationale

4.1 Rationale for study design

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

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Subject population	The study will enroll subjects with advanced/metastatic NSCLC which are EGFR wt, ALK negative, after failure of prior platinum doublet and checkpoint inhibitor administered for the treatment of the advanced stage. Subjects must be docetaxel naive. Subjects with targetable oncogenic drivers (such as EGFR-sensitizing mutations, or ALK translocation) will be excluded given the preferred approach for these subjects is targeted therapy with small-molecules. For more details on subject population, please refer to Section 5 .
Two-part study (Part 1: run-in and Part 2: randomized)	The randomized part will be preceded by a run-in in order to assess the safety, tolerability and preliminary efficacy of the combination of capmatinib and spartalizumab.
Comparator treatment	Docetaxel was selected as the comparator treatment as it is a globally established treatment in this pretreated setting, irrespective of the histology and has been used as a comparator in many phase III studies in the post-platinum setting.
Open-label	The trial is open-label for the following reasons: 1) double blinding would require two sets of i.v. administration for subjects due the difference in dosing schedules between the two arms, which would pose an unnecessary burden for the subject; and 2) effective blinding would be difficult, given the varying toxicities between the study treatments.
Stratification factors	Number of prior lines of therapy was chosen as a stratification factor due the expected difference in clinical outcome between subjects based on the number of prior lines of therapy received.
Randomization and 2:1 ratio	Subjects will be randomized as the efficacy of standard therapies, including docetaxel in this post-platinum doublet/post-checkpoint inhibitors setting is currently unknown with only anecdotal reports (Park and Cheung 2017 , Schvartsman et al 2017). The randomization 2:1 increases the chances for subjects to receive the innovative combination of immunotherapy and a MET inhibitor, which exhibits preclinical immunomodulatory properties and synergistic effect with immunotherapy. Furthermore, a 2:1 randomization ratio will allow for increased chance to detect adverse events with the capmatinib and spartalizumab combination.
Treatment beyond disease progression	This is to ensure those subjects (in either arm) who are clinically stable, tolerate the treatment, and are deriving clinical benefit can continue to receive treatment. Timely follow-up after the initial PD will ensure that subjects with confirmed/rapid progression will be discontinued and can initiate adequate subsequent therapies.

4.2 Rationale for dose/regimen and duration of treatment

4.2.1 Capmatinib in combination with spartalizumab

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](#)).

Glodde et al. 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-PD1 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-PD1 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 1.1.1](#)) further support the rationale for combining anti-PD1 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-PD1 antibodies will prevent suppression of T cell function through PD-L1 expressed on tumor cells or other immune cells.

The feasibility of the combination of capmatinib with a checkpoint inhibitor has already been confirmed in two studies ([CINC280X2108] and [CEGF816X2201C]). (For details, please refer to [Section 1.1.3.1](#) and [Section 1.1.3.2](#)).

The combination of capmatinib with spartalizumab has been evaluated in the study [CINC280X2108] (which used a fixed dose of spartalizumab 300 mg with a Q3W schedule) conducted in HCC where, based on the BLRM-EWOC (Bayesian Logistic Regression Model - Escalation With Overdose Control) model, the RP2D was declared at 400 mg BID for capmatinib in combination with 300 mg spartalizumab Q3W.

In the current study [CINC280D2201], the alternate dosing regimen of spartalizumab 400 mg Q4W will be used. Pharmacokinetic and safety data across dose levels in study [CPDR001X2101] supported the declaration of two RP2Ds, 300 mg Q3W and 400 mg Q4W for spartalizumab as a single agent. Based on the population PK model simulations, both regimens are expected to achieve similar exposure range at steady-state and achieve a mean steady-state C_{trough} value higher than the *ex vivo* EC50 for antigen-stimulated IL-2 production, a translational biomarker for PD-1 blockade (for additional information, please refer to [Section 1.1.2](#)). Two RP2Ds were chosen to allow more convenient scheduling of treatments for subjects receiving combination therapy with spartalizumab. In this study, a Q4W schedule has been chosen based on scheduling convenience in this setting of advanced NSCLC. The activity of docetaxel in the context of post-platinum and post-checkpoint inhibitor is unknown with anecdotal reports ([Park and Cheung 2017](#)[Schvartsman et al 2017](#)).

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

Docetaxel is an established treatment option for pretreated NSCLC subjects and has served as a control arm for several prospective, randomized trials in the second- or third-line setting including the most recent phase 3 studies with PD-(L)1 inhibitors (Herbst et al 2016, Rittmeyer et al 2017, Borghaei et al 2015, Brahmer et al 2015, Hanna et al 2004), and it is approved for the use in NSCLC irrespective of tumor histology. In the context of the post-platinum setting, a response rate of approximately 9-13%, median PFS of 3-4 months, and median OS of approximately 8-10 months is expected with docetaxel (Hanna et al 2004, Herbst et al 2016, Rittmeyer et al 2017, Borghaei et al 2015, Brahmer et al 2015). Overall, the reported response rates to second-line chemotherapy (including other single agent chemotherapeutics) have generally been < 11%, with median PFS and OS generally below 4 and 11 months, respectively (de Marinis and Grossi 2008, Weiss and Stinchcombe 2013, NCCN 2018, Novello et al 2016). Upon progression after second-line chemotherapy, subjects may be candidates for further treatment, although randomized evidence is scarce and most data come from phase II trials or retrospective analyses. Subjects often have limited response to third-line therapy, although it may have some palliative effect (Shepherd et al 2005, de Marinis and Grossi 2008, Eccles et al 2011, Reck et al 2014, Besse et al 2014, NCCN 2018). The activity of docetaxel in the context of post-platinum and post-checkpoint inhibitor is unknown with anecdotal reports (Park and Cheung 2017, Schvartsman et al 2017).

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

Subjects in this study have advanced non-small cell lung cancer and have progressed after one or two lines of prior approved chemotherapy, radiotherapy and/or immunotherapy. Given the clinical and molecular characteristics of their disease they have limited therapeutic options and the established standard, single agent chemotherapy regimens approved for this setting are of limited benefit.

Synergistic antitumor effect has been shown preclinically with capmatinib in combination with checkpoint inhibitors in non-MET driven tumor models. The safety profile of capmatinib and spartalizumab as monotherapies is well characterized (see [Section 1.1.1](#) and [Section 1.1.2](#)). This new combination has been proven to be safe at the dose of 400 mg BID capmatinib and spartalizumab 300 mg Q3W in HCC subjects treated in study [CINC280X2108] (see [Section 1.1.3.2](#)). The 24 weeks follow-up of this run-in phase is intended not only to allow a thorough assessment of the safety profile of this new schedule but also to assess the preliminary efficacy of this combination before enrolling more subjects into the randomized part.

Appropriate eligibility criteria and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for 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 may be minimized by compliance with the eligibility criteria and study procedures, as well as by close clinical monitoring.

As with any clinical study, there may be unforeseen risks with the combination studied, which could be serious. The specific risks for each compound are discussed below. For more details, refer to the toxicity data provided in the [capmatinib Investigator's Brochure] and in the [spartalizumab Investigator's Brochure]

4.5.1 Capmatinib

Based upon the clinical experience with capmatinib to date, the overall risk-benefit assessment of capmatinib is considered favorable with a manageable safety profile. Most of the AEs that have been reported, irrespective of relationship to study drug, have been manageable and generally mild or moderate in severity.

Caution is recommended when capmatinib is administered in combination with other anticancer drugs with a known risk of hepatotoxicity. One case of liver function test abnormal meeting Hy's Law criteria for hepatotoxicity (PHHO2015CN003025) has been reported for a subject enrolled in the NSCLC combination study with gefitinib [CINC280X2202]. The event could not be attributed solely to either drug alone or to the combination.

As of the IB cut-off of 28-Sep-2017, pneumonitis and ILD have been reported from both capmatinib single agent and combination studies with the 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.

For further information on potential toxicities, please refer to [Section 1.1.1](#) and 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.

Overall, clinical experience with spartalizumab to date suggests that it can cause irAEs. Immune-checkpoint inhibitors of this class may be associated with the occurrence of immune-mediated adverse events (irAE). In general, irAE 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) being typically the most frequent. Other immune-mediated AEs 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 epidermonecrosis or Steven 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, Brahmer et al 2018, Haanen et al 2017). In addition, mAb's 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 6.5.3.1](#) for further guidance).

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.

It is expected that spartalizumab would have a similar safety profile as other immune checkpoint inhibitors with the above-mentioned side effects possibly occurring in subjects treated with spartalizumab. For further detail on potential adverse events with spartalizumab treatment please refer to [Section 1.1.2](#) of this protocol.

4.5.3 Capmatinib combined with spartalizumab

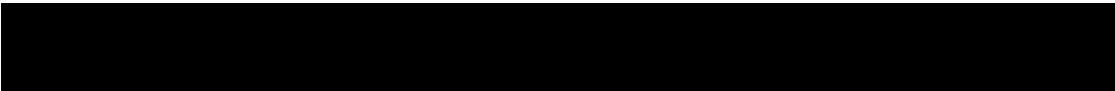
Pharmacokinetic drug-drug interaction (DDI) is anticipated to be low for the combination of capmatinib and spartalizumab.

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 between the compounds if given in combination. The combination is currently being evaluated in the dose escalation and expansion study [CINC280X2108] in subjects with hepatocellular carcinoma (HCC). To date, the safety profile of the combination in this disease setting has been manageable.

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.

4.5.4 Docetaxel

In this patient population, safety and efficacy of docetaxel has been well-established since its approval in 1996. Docetaxel is licensed as single agent and indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum chemotherapy. The median survival was 9.0 months with docetaxel versus 4.6 months for best supportive care (BSC) ($P = 0.016$). Quality-of-life analysis showed significant improvement in several disease-related symptoms in patients who received docetaxel.



The common adverse reactions to docetaxel are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions and myalgia.

Please refer to the current prescribing guidelines for docetaxel in this disease setting.

4.5.5 Risks of Imaging Procedures

Tumor assessments required by the trial include Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) scanning. There are both benefits and risks associated with the use of CT and MRI for imaging.

Contrast enhancement is a standard tool to evaluate potential metastatic lesions; subjects with contrast allergy are exempted from its use. The ordering physician should ensure that subjects are well hydrated and precautions taken to avoid renal injury due to contrast agents.

MRI is considered a very safe imaging modality; however, there is an underlying risk of potential injury to subjects due to the strong electromagnetic (EM) fields used in MRI scanning. Subjects with known metallic foreign bodies or implanted devices should not have MRI scans.

5 Population

The study population will include adult subjects with locally advanced (stage IIIB, not eligible for definitive chemo-radiation) or metastatic (stage IV) non-small cell lung cancer. Subjects must be docetaxel naive, and subjects with EGFR mutations and ALK rearrangement will be excluded.

To be eligible, patients must have progressed on prior treatment with a platinum doublet and a PD-L1 checkpoint inhibitor (either approved or investigational), either as single treatments (with the checkpoint inhibitor as last treatment) or in combination:

- Patients who have progressed after receiving a checkpoint inhibitor in combination with a platinum doublet, as first-line therapy.
- Patients who have progressed on anti-PD-(L)1 checkpoint inhibitor as second-line therapy, after receiving a platinum doublet as first-line therapy.
- Finally, patients who have received a checkpoint inhibitor as maintenance after platinum chemo-radiotherapy for stage III NSCLC and progressed to advanced stage within 12 months since the end of this therapy are also eligible.

Patients enrolled in this study are not permitted to participate in additional parallel investigational clinical 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. Written informed consent must be obtained prior to any screening procedures
2. Adult ≥ 18 years old at the time of informed consent

3. Histologically confirmed locally advanced/metastatic (stage IIIB or IV per AJCC/IASLC v. 8) NSCLC
4. Histologically or cytologically confirmed diagnosis of NSCLC that is both EGFR wt status and ALK- negative rearrangement status:
 - Patients with NSCLC of pure squamous cell histology can enter screening without EGFR mutation or ALK rearrangement testing or result; however, patients with pure squamous cell histology who are known to have EGFR mutations in exons 19 or 21 or ALK rearrangements will be excluded
5. Patients must have demonstrated progression of locally advanced/ metastatic NSCLC (stage IIIB, not amenable for definitive chemo-irradiation, or stage IV) following one prior platinum doublet and one prior PD-(L)1 checkpoint inhibitor (either alone or in combination)
 - Maintenance therapy given after first-line chemotherapy will be considered as part of the first-line therapy if given to patients with documented response or stable disease before starting the maintenance therapy.
 - Neo-adjuvant and adjuvant systematic therapies will count as one prior line of systemic treatment for the advanced stage if relapse occurred within 12 months from the end of the neoadjuvant or adjuvant systemic therapy.
 - The most recent line of therapy should include a PD-(L)1 checkpoint inhibitor (either alone or in combination)
6. Patients must be candidates for single agent chemotherapy with docetaxel
7. Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v5.0). Patients with any grade of alopecia are allowed to enter the study
8. At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation
9. Patients must have adequate organ function including the following laboratory values at the screening visit:
 - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ without growth factor support
 - Platelets $\geq 75 \times 10^9/L$
 - Hemoglobin (Hgb) $\geq 9 \text{ g/dL}$
 - Calculated creatinine clearance (using Cockcroft-Gault formula) $\geq 45 \text{ mL/min}$
 - Total bilirubin (TBIL) $\leq 1.5 \times \text{ULN}$ (upper limit of normal)
 - Aspartate transaminase (AST) $\leq 3 \times \text{ULN}$, except for patients with liver metastasis, who may only be included if AST $\leq 5 \times \text{ULN}$
 - Alanine transaminase (ALT) $\leq 3 \times \text{ULN}$, except for patients with liver metastasis, who may only be included if ALT $\leq 5 \times \text{ULN}$
 - Alkaline phosphatase (ALP) $\leq 5.0 \times \text{ULN}$
 - Asymptomatic serum amylase $\leq \text{Grade 2}$. Patients with Grade 1 or Grade 2 serum amylase at the beginning of the study must be confirmed to have no signs and/or

symptoms suggesting pancreatitis or pancreatic injury (e.g. elevated P-amylase, abnormal imaging findings of pancreas, etc.)

- Serum lipase \leq ULN
- Fasting plasma glucose \leq 160 mg/dL (\leq 8.9 mmol/L)

10. ECOG performance status (PS) of 0 or 1

11. Willing and able to comply with scheduled visits, treatment plan and laboratory tests

5.2 Exclusion criteria

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

1. Prior treatment with a MET inhibitor or HGF-targeting therapy
2. Any untreated central nervous system (CNS) lesion. However, patients are eligible if all known CNS lesions have been treated with radiotherapy or surgery and remained stable for \geq 4 weeks after treatment. Patients must be off corticosteroid therapy for \geq 2 weeks
3. Carcinomatous meningitis
4. 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) or intolerance to docetaxel excipients (as per local product label)
5. 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
6. Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 2 years. Exceptions to this exclusion include: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type
7. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GMCSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents \leq 2 weeks prior start of study treatment. If 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
8. Patients receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to Cycle 1 Day 1 and for the duration of the study:
 - Strong inhibitors of CYP3A4 (patients randomized to the docetaxel arm only will need to comply with this criterion for the whole duration of the study treatment)
 - Strong inducers of CYP3A4 (patients randomized to both capmatinib containing arm and docetaxel arm will need to comply with this criterion for the whole duration of the study treatment)
9. Use of any live vaccines against infectious diseases within 3 months of initiation of study treatment. Patients randomized to the spartalizumab containing arm will need to comply with this criterion for the whole duration of the study treatment
10. Patients receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of study treatment, and for the duration of the study. Patients on non-enzyme-inducing anticonvulsants are eligible

11. Systemic chronic steroid therapy (≥ 10 mg/day prednisone or equivalent) or any immunosuppressive therapy 7 days prior to planned date of first dose of study treatment. Topical, inhaled, nasal and ophthalmic steroids are allowed. Steroid premedication for docetaxel infusion does not apply
12. Concomitant medication(s) with a “Known Risk of Torsades de Pointes” per www.qtdrugs.org that cannot be discontinued or replaced by safe alternative medication.
13. Clinically significant, uncontrolled heart diseases:
 - Unstable angina within 6 months prior to screening
 - Myocardial infarction within 6 months prior to screening
 - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
 - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 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
 - Fridericia QT correction formula (QTcF) ≥ 470 ms on the screening Electrocardiogram (ECG) (as mean of triplicate ECG)
 - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
14. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting Cycle 1 Day 1 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 Cycle 1 Day 1, or patients who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions or radio-surgery for isolated brain lesions ≤ 2 weeks prior to Cycle 1 Day 1 is allowed
15. Major surgery within 4 weeks prior to starting study treatment (2 weeks for resection of brain metastases), or patients who have not recovered from the side effects of such a procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the study ≥ 1 week after the procedure
16. Impairment of GI function or GI disease that may significantly alter the absorption of capmatinib
17. 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, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
18. Previous anti-cancer and investigational agents within 4 weeks or $\leq 5 \times$ half-life of the agent (whichever is longer) before first dose of study treatment. If previous treatment is a monoclonal antibody or an anti PD-(L)1 checkpoint inhibitor, then the treatment must be

discontinued at least 4 weeks before first dose of study treatment. If previous treatment is an oral targeted agent, then the treatment must be discontinued at least 5 x half-life of the agent

19. History of allogenic bone marrow or solid organ transplant
20. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention)
21. Other severe, acute, or chronic medical or psychotic conditions or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results
22. Known history of testing positive for Human Immunodeficiency Virus (HIV) infection. Positive HIV test at screening where locally required
23. Patients with active hepatitis B infection (HBsAg positive) will be excluded. Note: patients with antecedent events of hepatitis B (anti-HBc positive, HBsAg and HBV DNA negative) are eligible. Patients with active hepatitis B (HBsAg positive) must receive antiviral treatment with lamivudine, tenofovir, entecavir, or other antiviral agents before the initiations of study treatment and show a suppressed viral replication (e.g. HBV DNA < 100 UI/ml) may be included. Indications for the screening/follow-up of hepatitis B and duration of prophylactic antiviral therapy should be dictated by institutional guidelines or specified in the protocol
24. Patients with positive test for hepatitis C ribonucleic acid (HCV RNA). Patients in whom Hepatitis C virus (HCV) infection resolved spontaneously (positive HCV antibodies without detectable HCV RNA) or those that achieved a sustained virological response after antiviral treatment and show absence of detectable HCV RNA \geq 6 months (with the use of IFN-free regimes) or \geq 12 months (with the use of IFN-based regimes) after cessation of antiviral treatment are eligible
25. Pregnant or nursing (lactating) women confirmed by a positive human chorionic gonadotrophin (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
26. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 150 days after stopping treatment with the spartalizumab in combination with capmatinib. For female patients treated with docetaxel, highly effective contraception must be used during the study and for at least 6 months after stopping docetaxel as per the locally approved package label. Highly effective contraception methods include:
 - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
 - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking

study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment

- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by laboratory assessment is she considered not of child bearing potential

27. Sexually active males unless they use a condom during intercourse while on treatment and during the follow-up periods mentioned below. Sexually active men should not father a child in these periods.

- Male subjects who receive treatment with spartalizumab in combination with capmatinib must use a condom during intercourse for 7 days after stopping treatment.
- Male subjects who receive treatment with docetaxel must use a condom during intercourse for at least 6 months after the last dose of docetaxel or as per the locally approved package label.

A condom is required to be used by vasectomized men as well during intercourse in order to prevent delivery of the drug via semen

28. Unable or unwilling to swallow tablets as per dosing schedule

29. Any other condition that would, in the investigator's judgment, contraindicate patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection, inflammation, intestinal obstruction, social/ psychological issues, etc.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

6 Treatment

6.1 Study treatment

For this study, the investigational drugs are capmatinib and spartalizumab. The study treatment is defined as capmatinib in combination with spartalizumab, or docetaxel. Both investigational drugs will be labeled and provided to sites by Novartis in compliance with legal requirements for each country. Docetaxel will be procured locally as it is commercially available in each participating country.

6.1.1 Investigational and control drugs

The treatment period begins on Cycle 1 Day 1. In other words, the first dose of study drug (capmatinib plus spartalizumab or docetaxel) is given on Day 1 of Cycle 1. Cycle 1 Day 1 should occur no later than 3 days after registration into the IRT (Interactive Response Technology) system.

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

Table 6-1 Investigational and control drugs

Investigational/Control Drugs (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Drug package	Supplier (global or local)
Capmatinib (INC280) 150 mg or 200 mg	Film-coated tablet	Oral use	Open-label subject specific; bottles	Global
Spartalizumab (PDR001) 100 mg	Concentrate for solution for infusion	Intravenous use	Open-label subject specific; 4 x 100 mg vials	Global
Docetaxel (as per local product available)	Concentrate for solution for infusion	Intravenous use	Open-label bulk supply; vials	Local

6.1.2 Additional study treatments

Spartalizumab (Infusion Reactions)

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 standard of care, at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status.

If a subject experiences a Grade 3 infusion or anaphylactic/anaphylactoid reaction, the subject will discontinue spartalizumab treatment. Further guidelines on management of spartalizumab infusion reactions are provided in [Section 6.5.3](#).

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.

Docetaxel

Pre-medication schemes should follow local guidelines as per standard of care and product labels.

6.1.3 Treatment arms/group

Part 1: Run-in

In the run-in part of the study, subjects will be treated with capmatinib and spartalizumab as described below.

- **Combination of capmatinib and spartalizumab**

- Capmatinib 400 mg (tablets) orally twice daily (BID) with or without food followed by spartalizumab 400 mg intravenously (i.v.) every 28 days
- Capmatinib will be given as continuous daily dosing, and the first dose is administered at the study center.
- Spatalizumab will be administered on Day 1 of each 28 day cycle.
- A complete cycle of treatment is defined as 28 days of continuous capmatinib treatment and an infusion of spatalizumab every 28 days.

Part 2: Randomized

In the randomized part of the study, subjects will be assigned at Cycle 1 Day 1 to one of the following two treatment arms/groups in a ratio of 2:1 according to stratification.

- **Arm 1: Combination of capmatinib and spartalizumab**

- Capmatinib 400 mg (tablets) orally twice daily (BID) with or without food followed by spartalizumab 400 mg intravenously (i.v.) every 28 days
- Capmatinib will be given as continuous daily dosing, and the first dose is administered at the study center
- Spatalizumab will be administered on Day 1 of each 28 day cycle
- A complete cycle of treatment is defined as 28 days of continuous capmatinib treatment and an infusion of spatalizumab every 28 days.

- **Arm 2: Reference chemotherapy**

- Docetaxel 75 mg/m² intravenously (i.v.) following local guidelines as per standard of care and product labels (including steroid premedication)
- First infusion day defines Cycle 1 Day 1
- Administered every 21 days
- A complete cycle of treatment is defined as an infusion of docetaxel every 21 days.

6.1.4 Guidelines for continuation of treatment

Guidelines on the management of common capmatinib-, spartalizumab- and docetaxel-associated toxicities and dose modification instructions are provided in [Section 6.5.3](#).

6.1.5 Treatment duration

Subjects will continue capmatinib and spartalizumab combination (for both Part 1: run-in and Part 2: randomized) or docetaxel until they experience any of the following: documented disease progression by RECIST 1.1 as assessed by the investigator, withdrawal of consent,

pregnancy, lost to follow-up, or death irrespective of start of new anti-neoplastic therapy. Please refer to [Section 9.1](#).

Crossover is not allowed.

6.1.5.1 Treatment beyond disease progression

Clinical data indicate that in some cases subjects may derive benefit from continuing study treatment despite initial evidence of disease progression.

Subjects will be permitted to continue study treatment beyond initial disease progression as per RECIST 1.1 until study treatment discontinuation criteria are met as per [Section 9.1](#) provided they meet 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
- Separate informed consent for treatment beyond disease progression is provided by the subject

Capmatinib and spartalizumab combination

Subjects who meet the above criteria and continue study treatment beyond initial disease progression per RECIST 1.1 [REDACTED] (see [Section 16.2](#)) and continue all study procedures as outlined in [Table 8-2](#).

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

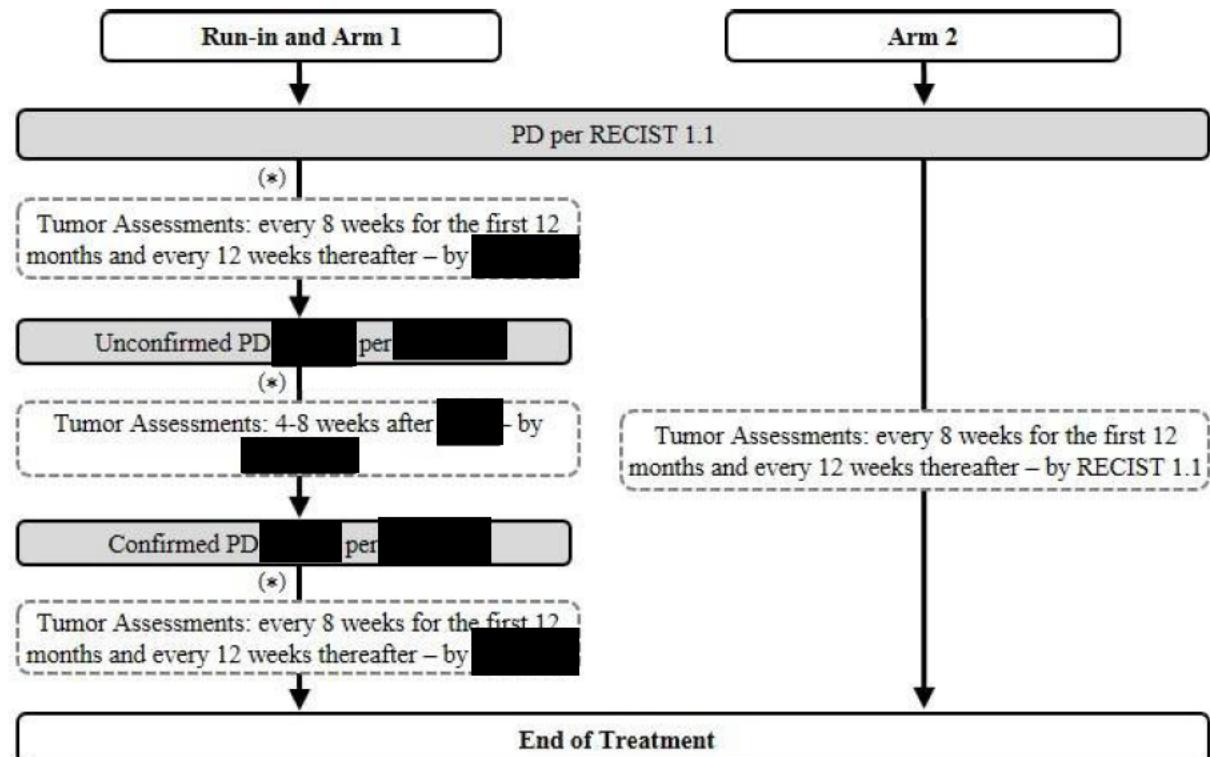
Docetaxel

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 8-3](#).

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. Subjects who are no longer deriving clinical benefit or who meet other protocol discontinuation criteria must be discontinued.

Please refer to [Section 8.3](#) for additional information on RECIST 1.1, and refer to Figure for an overview of treatment beyond progression.

Figure 6-1 Optional Treatment Beyond Disease Progression



(*) Subjects should meet 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
- Separate informed consent for treatment beyond disease progression is provided by the subject

6.2 Other treatment(s)

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapy deemed necessary for the care of the subject (e.g. such as anti-emetics, anti-diarrhea) is permitted 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 drug. All medications (excluding study treatment and prior antineoplastic treatments), blood transfusions, surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose administration of capmatinib and spartalizumab combination or docetaxel through 30 days after the last dose of capmatinib and spartalizumab combination or docetaxel will be recorded in the concomitant medications or surgical and medical procedures eCRF, respectively. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications, food supplements and vitamins.

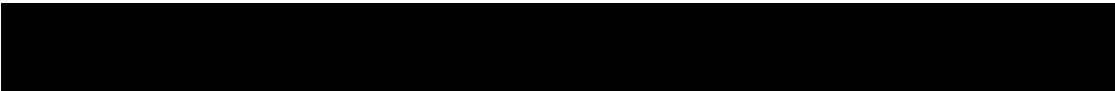
The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to subjects
- No anticancer agents other than the study medication (capmatinib and spartalizumab combination or docetaxel) should be given to subjects.

Subjects are permitted to use the following medications while taking capmatinib and spartalizumab combination:

- Oral or topical antibiotics
- Medications to prevent or treat nausea, vomiting or diarrhea
- 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.
- Treatment with bisphosphonates (please refer to [Section 6.2.1.2](#))
- Oxygen therapy and blood products or transfusions
- Local radiotherapy (please refer to [Section 6.2.1.2](#))
- Anti-diarrheal medications (e.g., loperamide) for subjects who develop diarrhea
- Pain medication to allow the subject to be as comfortable as possible
- Immunosuppressive agents to treat suspected irAEs
- Nutritional support or appetite stimulants (e.g. megestrol)
- Inactivated vaccines
- Topical, inhaled, nasal and ophthalmic steroids are allowed.

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



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

- Capmatinib is a moderate CYP1A2 inhibitor. Coadministration of capmatinib increased sensitive CYP1A2 probe substrate (caffeine) AUC by 135% (see [Section 1.1.1](#)). The dose of CYP1A2 substrates with a narrow therapeutic index may need to be reduced when used concurrently with capmatinib as capmatinib may increase their exposure. Consult the product information of the concomitant drug for dose adjustment.
- Coadministration 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) (please refer to [Section 1.1.1](#)). Monitor subjects closely for symptoms of increased exposure to Pgp or BCRP substrates. Consult the concomitant Pgp or BCRP substrate product information when considering dose adjustment.
- Coadministration of capmatinib with a strong CYP3A4 inhibitor (itraconazole) increased capmatinib AUC by 42%. There is no change in capmatinib Cmax. Execute caution when use strong CYP3A4 inhibitors concurrently with capmatinib.
- While the data on the concurrent use of PPI and food have to be considered preliminary as they have been generated in a small cohort of subjects of the study [CINC280A2108], the decrease in exposure imposes caution on the use of PPI when capmatinib is taken.
- Short acting gastric acid modulators containing aluminum hydroxide and magnesium hydroxide, or calcium carbonate can be taken; however, it is recommended to take these drugs at least 1 hour before or 2 hours after administration of capmatinib.
- H2 receptor antagonists should be used with caution. If subjects are using H2 receptor antagonists during the course of this study, capmatinib should be administered at least 3 hours before or 6 hours after taking H2 receptor antagonists.
- Capmatinib is a weak- to-moderate inhibitor of CYP2C8, CYP2C9 and CYP2C19 *in vitro*. Substrates of CYP2C8, CYP2C9 and CYP2C19 with a narrow therapeutic window should be administered with caution.

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

Table 6-2 Capmatinib: drugs to be used with caution during co-administration

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, neflifavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
CYP1A2 substrate with NTI	theophylline, tizanidine
CYP2C9 substrate with NTI	(S)-warfarin
CYP2C19 substrate with NTI	(S)-mephénytoïn

Mechanism of Interaction	Drug Name
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, proguanil, posaconazole, pravastatin, ranolazine, ritonavir, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
BCRP substrates	atorvastatin daunorubicin, dolulegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitor	esomeprazole, pantoprazole, omeprazole, lansoprazole, rabeprazole, dexlansoprazole
H ₂ -receptor antagonists	ranitidine, nizatidine, famotidine, cimetidine
Antacids	aluminum hydroxide, aluminum carbonate, calcium hydroxide, calcium carbonate, bismuth subsalicylate
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies".	
NTI: narrow therapeutic index	

6.2.1.1.2 Spatalizumab: permitted concomitant therapy requiring caution and/or action

If a subject is using erythropoiesis stimulating agents (ESAs) prior to enrollment (at least 2 weeks before start of study treatment), he/she may continue the treatment.

Anticoagulation and anti-aggregation agents are permitted if the subjects are already at stable doses for > 2 weeks at time of first dose 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 sampling according to the institutional guidelines.

Topical, inhaled, nasal and ophthalmic steroids are allowed.

6.2.1.1.3 Docetaxel: permitted concomitant therapy requiring caution and/or action

Please follow local guidelines as per standard of care and product labels.

6.2.1.2 Use of bisphosphonates and local radiotherapy

Treatment with bisphosphonates for pre-existing bone metastases is permitted, if clinically indicated, and following existing local guidelines and documented discussion with Novartis. Treatment with bisphosphonates should preferably begin before the study treatment is initiated, but can also be initiated during therapy only if absence of radiological bone disease progression

is well documented (in this case, the reason for its use must be clearly documented; i.e. “pre-existing, non-progressing, bone metastases”).

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

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 modulate the immune responses; however, limited-field palliative radiotherapy may be allowed as a concomitant therapy (see [Section 6.2.1.2](#)).

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

6.2.2.1 Capmatinib: prohibited medication

Coadministration of capmatinib with a strong CYP3A4 inducer (rifampicin) has decreased capmatinib AUC by 67% and Cmax by 56%. Concurrent use of strong CYP3A4 inducers should be prohibited as decreased capmatinib exposure may lead to reduced efficacy [capmatinib Investigator's Brochure].

The prohibited medications are listed in the [Table 6-3](#) below.

Drugs with a known risk of Torsades de Pointes (TdP) are prohibited. For identification of drugs with known risk of TdP please refer to www.qtdrugs.org (refer to [Table 6-4](#)).

Table 6-3 Capmatinib: prohibited drugs

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

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

Table 6-4 Drugs with a known risk of Torsades de Pointes

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

TdP Risk	Generic Names
Check crediblemeds.org/healthcare-providers/drug-list for the most updated list.	

6.2.2.2 Spartalizumab: prohibited medication

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of infusion reaction, irAEs, and for prophylaxis against imaging contrast dye allergy, standard pre-medication for chemotherapy or replacement-dose steroids in the setting of adrenal insufficiency (providing this is < 10 mg/day prednisone or equivalent), or transient exacerbations of other underlying diseases such as COPD requiring treatment. If systemic corticosteroids are required for the control of infusion reactions or irAEs, it must be tapered and be at non-immunosuppressive doses (< 10 mg/day of prednisone or equivalent) before 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 and capmatinib must be discontinued (note: next dose of spartalizumab can be delayed up to 12 weeks).

The use of live vaccines is not allowed through the whole duration of the study. Inactivated vaccines are allowed.

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

6.2.2.3 Docetaxel: prohibited medication

Please follow local guidelines as per standard of care and product labels.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis/sponsor 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 (ICF), the subject is assigned to the next sequential Subject No. available.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject. In case of re-screening a new Subject No. will be assigned to patient through the Clinical Data Management System interface and this new Subject No. will be provided to IRT for registration as re-screened patient. If the subject fails to be randomized or start treatment for any reason, the reason will be entered into the disposition page.

6.3.2 Treatment assignment, randomization

Prior to dosing, for all subjects who fulfill all inclusion/exclusion criteria, the investigator or his/her delegate will log on to the IRT system and confirm that the subject fulfills all the

inclusion/exclusion criteria by completing the key eligibility criteria checklist embedded in the system.

Part 1: Run-in

During the run-in part, approximately 15 subjects will be enrolled via IRT for treatment with capmatinib and spartalizumab combination.

Part 2: Randomized

During the randomized part, approximately 90 subjects will be randomized via IRT to one of two treatment arms (capmatinib plus spartalizumab [n=60] or docetaxel [n=30]) in a 2:1 ratio.

During the randomized part, 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 a unique medication number for the first package of study treatment to be dispensed to the subject. The randomization number will not be communicated to the investigator or his/her delegate. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. 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. Random permuted blocks scheme will be used for this study. The randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Global Clinical Supplies using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments. Randomization will be stratified by the number of prior lines of therapy received. Please refer to [Table 6-5](#) for the number of prior lines of therapy received.

During Part 1 and Part 2 of the study, the study treatment phase begins on Cycle 1, Day 1 with the first administration of capmatinib and spartalizumab combination or the first administration of docetaxel. Cycle 1 Day 1 should occur no later than 3 days after registration into IRT system.

Table 6-5 Number of prior lines of systemic therapy

Number of prior systemic therapies for eligibility and stratification factors	Definition
Treatment, which counts as chemotherapy for advanced/ metastatic disease	Platinum chemotherapy for stage IIIB/IV NSCLC Adjuvant/ neoadjuvant platinum chemotherapy and progressed within 12 months of end of therapy.
Treatment, which doesn't count as chemotherapy for advanced/ metastatic disease	Adjuvant/ neoadjuvant platinum chemotherapy and progressed > 12 months of end of therapy.
Eligible number of prior therapies	Eligible patients must have received one platinum chemotherapy AND one PD-(L)1 inhibitor
Enrolled as 2nd line population	Platinum based chemotherapy and PD-(L)1 inhibitor were received concurrently or there was no PD between chemotherapy and PD-(L)1 inhibitor (therefore counted as one line)
Enrolled as 3rd line population	Platinum based chemotherapy and PD-(L)1 inhibitor were received as sequential therapies. There was a PD between chemotherapy and PD-(L)1 inhibitor

6.4 Treatment blinding

Treatment assignment will be open to subjects, investigator staff, persons performing the assessments, and the Novartis representatives from the Clinical Trial Team.

6.5 Dose escalation and dose modification

No dose escalations are permitted.

6.5.1 The run-in review meeting

To assess the safety and tolerability of capmatinib and spartalizumab combination as well as preliminary efficacy prior to the randomized part of the study, the run-in part of the study will enroll approximately 15 subjects who will be treated with the capmatinib 400 mg (BID) and spartalizumab 400 mg intravenously (i.v.) once every 28 days.

Subjects will be considered evaluable for tolerability decision if the subject:

- has received at least 1 infusion of spartalizumab and taken at least 50% of the planned dose of capmatinib in the first 56 days (8 weeks) of treatment and
- has safety assessments for a minimum of 56 days (8 weeks) or has had a DLT during the first 8 weeks.

A review meeting will take place after all subjects have at least 24 weeks of follow-up. Decision on tolerability will be made by Investigators and Novartis study personnel. The decisions will be based on a synthesis of all relevant data available including safety information, DLTs, all CTCAE v5.0 \geq Grade 2 toxicity data during the first 8 weeks (56 days) of the study treatment, pharmacokinetic data and preliminary efficacy data from evaluable subjects. The decision will be guided by the BLRM with EWOC principle evaluating the probability of DLT from all subjects enrolled in the run-in prior to opening the randomized phase. In particular, overall safety will be assessed in the context of the known safety data generated with the capmatinib and spartalizumab combination and will be used for decisions prior to opening the randomized phase.

6.5.1.1 Implementation of safety and tolerability decisions

To implement tolerability decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs) and the recommendations from the BLRM will be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference.

6.5.1.2 Implementation of dose escalation decisions

Not applicable.

6.5.1.3 Intra-Subject dose escalation

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

6.5.2 Definitions of dose limiting toxicities (DLTs)

A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs during the first 56 days (8 weeks) of treatment with capmatinib and spartalizumab and meets any of the criteria included in [Table 6-6](#). The National Cancer Institute Common Terminology Criteria for Adverse events (NCI-CTCAE) v5.0 will be used for all grading. For the purpose of tolerability decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities.

Criteria for defining dose limiting toxicities (DLTs)

Table 6-6 Criteria for defining dose limiting toxicities (DLTs)

TOXICITY	DLT CRITERIA
Blood and lymphatic system disorders	Anemia CTCAE Grade 4 Thrombocytopenia Grade 3 with clinically significant bleeding Thrombocytopenia CTCAE grade 3 (for ≥ 7 consecutive days) Thrombocytopenia Grade 4 Neutropenia Grade 3 (for ≥ 7 consecutive days) Neutropenia Grade 4 Febrile neutropenia CTCAE Grade ≥ 3
Cardiac	Grade ≥ 3 or cardiac event that is symptomatic or requires medical intervention Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Grade ≥ 3 Troponin elevation QTc interval prolonged Grade ≥ 3 (QTcF ≥ 501 ms) on at least two separate ECGs for > 7 consecutive days
Vascular disorders/Hypertension	Persistent hypertension CTCAE Grade 3 requiring more than one drug or more intensive therapy than previously administered. Grade 4 Hypertension (any duration)
Gastrointestinal	Nausea and vomiting: <ul style="list-style-type: none">• CTCAE grade ≥ 3 > 48 hours despite standard anti-emetics• CTCAE grade 4 Diarrhea: <ul style="list-style-type: none">• Recurrence of CTCAE grade 2 (despite anti-diarrheal treatment)• CTCAE grade ≥ 3 > 48 hours despite maximal anti-diarrheal treatment• CTCAE grade 4
Skin and subcutaneous tissue	Rash / photosensitivity CTCAE Grade ≥ 3 for > 7 consecutive days despite skin toxicity treatment Stevens-Johnson syndrome, toxic epidermal necrolysis and other serious or life-threatening skin reactions.
Hyperglycemia	Hyperglycemia Grade 3 (FPG $> 250 - 500$ mg/dL) for > 7 consecutive days despite anti-diabetic treatment Hyperglycemia Grade 4 (FPG > 500 mg/dL) Hyperglycemia leading to diabetic keto-acidosis, hospitalization for intravenous insulin infusion, or non-ketotic coma.
Infection	CTCAE grade 3 infection or fever in the absence of neutropenia if they persist > 5 days. CTCAE Grade 4 infection of any duration.
Pneumonitis (interstitial lung disease)	<ul style="list-style-type: none">• CTCAE Grade 2 pneumonitis if it persists > 7 days despite treatment with corticosteroids.• Grade 3-4 pneumonitis of any duration

TOXICITY	DLT CRITERIA
Metabolism and nutrition disorders: Calcium-phosphate heterostasis tCa x Pi increase	<ul style="list-style-type: none"> • tCa x Pi $> 55 \text{ mg}^2/\text{dL}^2 \leq 70 \text{ mg}^2/\text{dL}^2$ for > 7 consecutive days • tCa x Pi $> 70 \text{ mg}^2/\text{dL}^2$
Fatigue/Asthenia	• Fatigue/Asthenia CTCAE grade ≥ 3 and lasting > 7 consecutive days is a DLT
Immune-related toxicities (except pneumonitis)	<ul style="list-style-type: none"> • CTCAE Grade 3 immune-related toxicities that persist > 14 days with same severity despite treatment with corticosteroids. • Immune-related toxicities CTCAE Grade 4 of any duration
Other Adverse Events	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in cycles 1 and 2, may be considered to be DLTs by the Investigators and Novartis, even if not CTCAE grade 3 or higher.
Investigations	<p>Isolated total bilirubin* $> 1.5 – 3.0 \times \text{ULN}$ for > 7 days</p> <p>Isolated total bilirubin* $> 3.0 \times \text{ULN}$</p> <p>Isolated AST or ALT* $> 5.0 – 10.0 \times \text{ULN}$ for subjects with baseline value $\leq 3 \times \text{ULN}$ ($> 10.0 – 20.0 \times \text{ULN}$ for subjects with liver metastases and baseline value $> 3.0 – 5.0 \times \text{ULN}$) for > 7 days</p> <p>Isolated AST or ALT* $> 10.0 \times \text{ULN}$ for subjects with baseline value $\leq 3 \times \text{ULN}$ ($> 20.0 \times \text{ULN}$ for subjects with liver metastases and baseline value $> 3.0 – 5.0 \times \text{ULN}$)</p> <p>For subjects with normal baseline AST and ALT and total bilirubin value: AST or ALT $> 3.0 \times \text{ULN}$ combined** with total bilirubin $> 2.0 \times \text{ULN}$ without evidence of cholestasis***</p> <p>OR</p> <p>For subjects with abnormal baseline AST or ALT or total bilirubin value: [AST or ALT $> 2 \times \text{baseline}$ AND $> 3.0 \times \text{ULN}$] OR [AST or ALT $> 8.0 \times \text{ULN}$], whichever is lower, combined with [total bilirubin $> 2 \times \text{baseline}$ AND $> 2.0 \times \text{ULN}$]</p> <p>Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 3 > 7 consecutive days</p> <p>Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 4</p> <p>Serum creatinine CTCAE Grade ≥ 3</p> <p>Serum CK/CPK CTCAE Grade ≥ 3 for > 7 consecutive days</p> <p>Serum CK/CPK CTCAE Grade 4</p> <p>Symptomatic serum amylase or lipase elevation, requiring medical intervention.</p>

**"Isolated total bilirubin" increase defined as: total bilirubin increase without ALT or AST increase; "isolated AST or ALT" increase defined as: AST or ALT increase without total bilirubin increase

***"Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

****"Cholestasis" defined as: ALP elevation [$> 2.0 \times \text{ULN}$ and 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)

6.5.3 Dose modifications

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

There are no dose reductions allowed in this study for spartalizumab. Dose interruptions for spartalizumab are permitted per [Section 6.5.3.1](#).

Dose reductions and interruptions are permitted for capmatinib per [Section 6.5.3.1](#).

Dose reductions and interruptions are permitted for docetaxel per the investigator's judgment and local guidelines. Please refer to [Section 6.5.3.2](#).

Permanent treatment discontinuation is mandatory for specific events as indicated in [Section 6.5.3.1](#) (capmatinib and spartalizumab subjects) and [Section 6.5.3.2](#) (docetaxel subjects).

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

6.5.3.1 Capmatinib/Spartalizumab dose modifications

Capmatinib dose reduction will follow the dose reduction steps described in [Table 6-7](#). For each subject, a maximum of two dose level modifications is allowed after which the subject must be discontinued from treatment with capmatinib. The lowest dose allowed, 200 mg BID in tablets, is expected to be pharmacologically active, as the observed steady state plasma trough concentrations ([CINC280X1101], [CINC280X2202], n=6) were above the concentration associated with full MET inhibition in xenograft mice models (IC90, 120 nM total concentration).

Table 6-7 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

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

No changes in dose of spartalizumab are allowed.

Overall, subjects with AEs suspected to be related to spartalizumab, including those of potential immune-mediated etiology (irAE), may need to interrupt or permanently discontinue study treatment as outlined in this section. In general, study treatment must be permanently discontinued in case of:

- Any life-threatening adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy)
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to \leq Grade 1
- Inability to reduce the dose of steroids (for the management of irAE) to 10 mg/day or less of prednisone or equivalent (or as indicated in the tables below) within 12 weeks
- Any severe or Grade 3 recurring treatment-related adverse reaction

The 12 weeks' timeframe will begin from the time the irAE reaches a grade that leads to spartalizumab interruption. Investigators should refer to the latest [capmatinib Investigator's Brochure] and [spartalizumab Investigator's Brochure] for additional information regarding the background of capmatinib and spartalizumab and the management of other AEs or potential safety-related issues not specifically mentioned in the protocol.

Identification and management requirement for AEs of potential immune-mediated etiology (irAE)

Adverse events of special interest (AESI) include AEs of a potential immune-mediated etiology (irAE) that are associated with spartalizumab treatment. Investigators must be vigilant and carefully identify AEs that may be suggestive of potential irAEs as their appearance may be sub-clinical and early diagnosis is critical for its adequate management and resolution. Collaboration with disease-specific subspecialties is encouraged; corticosteroids are the mainstay of treatment for most irAEs.

An irAE may be of low grade and self-limited, most frequently involving the GI tract (i.e. diarrhea/colitis), skin (i.e. rashes), liver (i.e. hepatitis), lung (i.e. pneumonitis), kidneys (i.e. nephritis) and endocrine systems (e.g. hypothyroidism, hyperthyroidism, type I diabetes, hypophysitis including hypopituitarism and adrenal insufficiency variety of endocrinopathies). Other immune-mediated AEs 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 epidermonecrosis or Steven 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). However, nearly all organs can be affected by immune-mediated toxicities. irAEs often occur relatively early (mostly within weeks to 3 months after treatment initiation), however, may develop at any time during treatment (even after several months), and may also occur after treatment discontinuation.

Serological, immunological and histological assessments should be performed as deemed appropriate by the investigator, to verify the potential immune-related nature of the AE, and exclude a neoplastic, infectious or metabolic origin of the AE.

Severe grade or persistent lower grade irAEs typically require interrupting or permanently discontinuing treatment and administration of systemic steroids, and sometimes other immunosuppressive medications (i.e. tumor necrosis factor alpha antagonists, mycophenolate or tacrolimus, etc.). Early recognition and work-up of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants. Some events like endocrinopathies may require life-long hormonal replacement. Tapering of steroids should not be too rapid to avoid recurrence or worsening of irAEs. The management of irAEs may further include initiation of antibiotics for prophylaxis against opportunistic infections.

Subjects should be instructed to return to the study site as soon as possible (instead of waiting for their next scheduled visit) if they experience symptoms consistent with an irAE. Patients who experience a new or worsening irAE should be contacted and/or evaluated by the study site more frequently.

Based on experience and published guidelines on the management of irAEs in patients treated with immune checkpoint inhibitors ([Brahmer et al 2018](#), [Haanen et al 2017](#), [NCCN 2018](#)), instructions have been developed regarding how to manage irAEs that may occur in subjects receiving spartalizumab. Dose modification requirements and AE management guidelines for the potential irAEs are provided in the following tables: haematological ([Table 6-8](#)), renal

(Table 6-9), hepatic (Table 6-10), metabolic (Table 6-11), cardiac (Table 6-12), gastrointestinal (Table 6-13), skin and subcutaneous tissue (Table 6-14), respiratory, thoracic and mediastinal (Table 6-15), endocrine (Table 6-16), general and administration site (Table 6-17), other potential immune-related adverse events (Table 6-18). Any Grade 4 irAE must result in permanent discontinuation of spartalizumab. In addition, guidance for management of spartalizumab-infusion reaction and cytokine release syndrome is provided in Table 6-18.

Investigators are encouraged to contact the Sponsor as needed to discuss cases that warrant separate discussion outside of the scope of the current instructions.

The dosing modification requirements are mandatory, however, the AE management guidelines are recommendations and can be modified according to the local practices.

Table 6-8 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for Haematological Adverse Events

Hematological Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Neutrophil Count Decreased (NCI-CTCAE v5.0)		
Grade 1 (ANC < LLN - 1500/mm ³ ; < LLN - 1.5 x 10 ⁹ /L)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	• Treat per local/institutional guidelines
Grade 2 (ANC < 1500 - 1000/mm ³ ; < 1.5 - 1.0 x 10 ⁹ /L)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	• Treat per local/institutional guidelines
Grade 3 (ANC < 1000 - 500/mm ³ ; < 1.0 - 0.5 x 10 ⁹ /L)	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, resume capmatinib and spartalizumab treatment at the same dose level and schedule If resolved in > 7 days, then restart capmatinib at ↓ 1 dose level and spartalizumab at the normal dose and schedule.	• Treat per local/institutional guidelines
Grade 4 (ANC < 500/mm ³ ; < 0.5 x 10 ⁹ /L)	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, resume capmatinib and spartalizumab treatment at the same dose level and schedule If resolved in > 7 days, then restart capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule.	• Treat per local/institutional guidelines
Febrile Neutropenia (ANC < 1000/mm ³ (< 1.0 x 10 ⁹ /L), fever > 38.3°C)	Mandatory: omit capmatinib and spartalizumab dose level until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, then restart capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule. If resolved in > 7 days, discontinue subject from all study drug treatments	• Treat per local/institutional guidelines
Platelet Count Decreased (Thrombocytopenia) (NCI-CTCAE v5.0)		
Grade 1 (PLT < LLN - 75,000/mm ³ ; < LLN - 75 x 10 ⁹ /L)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	• Treat per local/institutional guidelines

Hematological Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Grade 2 (PLT < 75,000 - 50,000/mm ³ ; < 75 - 50 x 10 ⁹ /L)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	<ul style="list-style-type: none"> • Treat per local/institutional guidelines
Grade 3 (PLT < 50,000 - 25,000/mm ³ ; < 50 - 25 x 10 ⁹ /L)	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, resume capmatinib and spartalizumab treatment at the same dose level and schedule If resolved in > 7 days, then restart capmatinib at ↓ 1 dose level and spartalizumab at the normal dose and schedule.	<ul style="list-style-type: none"> • Treat per local/institutional guidelines
Grade 4 (PLT < 25,000/mm ³ ; < 25 x 10 ⁹ /L)	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, restart capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule. If resolved in > 7 days, permanently discontinue subject from all study drug treatments	<ul style="list-style-type: none"> • Treat per local/institutional guidelines
Hemoglobin Decreased (Anemia) (NCI-CTCAE v5.0)		
Grade 1 (Hgb < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	<ul style="list-style-type: none"> • Treat per local/institutional guidelines
Grade 2 (Hgb < 10.0 - 8.0 g/dL; < 6.2 - 4.9 mmol/L; < 100 - 80 g/L)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	<ul style="list-style-type: none"> • Treat per local/institutional guidelines
Grade 3 (Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L)	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, resume capmatinib and spartalizumab treatment at the same dose level and schedule If resolved in > 7 days, then restart capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule.	<ul style="list-style-type: none"> • Treat per local/institutional guidelines
Grade 4 (Life – threatening consequences, urgent intervention indicated)	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, resume capmatinib and spartalizumab treatment at the same dose level and schedule If resolved in > 7 days, then restart capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule. If toxicity recurs, permanently discontinue subject from all study drug treatments	<ul style="list-style-type: none"> • Treat per local/institutional guidelines
Autoimmune hemolytic anemia, hemolytic uremic syndrome, or acquired hemophilia grade ≥ 3	Mandatory: permanently discontinue subject from all study drug treatments	<ul style="list-style-type: none"> • Consult with specialist • Consider systemic corticosteroids and other therapies as appropriate (e.g. transfusion) per

Hematological Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
		local institutional guidelines

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

Table 6-9 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for Creatinine Increases

Renal Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Creatinine Increased (NCI-CTCAE v5.0)		
Grade 1 (> ULN - 1.5 x ULN)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	<ol style="list-style-type: none"> 1. Monitor creatinine weekly 2. If creatinine returns to baseline resume routine creatinine monitoring per protocol 3. Promote hydration 4. Consider cessation of nephrotoxic drugs
Grade 2 (> 1.5 - 3.0x baseline, >1.5-3.0 x ULN)	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume treatment at same dose level and schedule	<ol style="list-style-type: none"> 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) <p>If worsening or no improvement: 1 to 2 mg/kg/d prednisone or equivalents</p>
Grade 3 (>3 x baseline, > 3.0 - 6.0 x ULN) AND Grade 4(> 6.0 x ULN)	Mandatory: Permanently discontinue subject from all study drug treatments	<ol style="list-style-type: none"> 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

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

Table 6-10 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for liver laboratory alterations

Hepatic Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Blood Bilirubin Increased ^d (NCI-CTCAE v5.0)		
Grade 1 (> 1.5 x ULN if baseline was normal; >1.0- 1.5 x ULN if baseline was abnormal)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	<ul style="list-style-type: none"> • Monitor LFTs per protocol or more frequently if clinically indicated

Hepatic Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Grade 2 (> 1.5 - 3.0 x ULN if baseline was normal; > 1.5 - 3.0 x ULN if baseline was abnormal)	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then restart capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule.	<ul style="list-style-type: none"> • Frequent monitoring of LFTs, (every 2-3 days) until resolved to ≤ 1.5 x ULN • Rule-out alternative causes (e.g. concomitant medications, infection, disease progression)
Grade 3 (> 3.0 - 10.0 x ULN if baseline was normal; > 3.0 - 10.0 x ULN if baseline was abnormal)	Mandatory: permanently discontinue subject from all study drug treatments	<ul style="list-style-type: none"> • Frequent monitoring of LFTs, (every 2-3 days), until resolved to ≤ baseline. 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 (> 10.0 x ULN baseline was normal; > 10.0 x ULN baseline was abnormal)	Mandatory: permanently discontinue subject from all study drug treatments	<ul style="list-style-type: none"> • 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 baseline or stabilization over 4 weeks. See additional recommendation below for AST/ALT Grade 3/4.
Isolated AST or ALT Elevation (Alanine Aminotransferase Increased or Aspartate Aminotransferase Increased) (NCI-CTCAE v5.0)		
Grade 1 (> 3.0 x ULN if baseline was normal; > 1.5 - 3.0 x ULN if baseline was abnormal)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	Treat per local/institutional guidelines
Grade 2 (> 3.0 - 5.0 x ULN if baseline was normal; > 3.0 - 5.0 x ULN if baseline was abnormal)	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then restart capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule. Patients with baseline grade 2 AST/ALT value (>3.0-5.0 x ULN) may continue treatment	<ul style="list-style-type: none"> • For subjects with baseline value ≤ 3.0 x ULN: repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeated test, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN • For subjects with baseline value > 3.0 - 5.0 x ULN: monitor LFTs per protocol or more frequently if clinically indicated

Hepatic Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Grade 3 (> 5.0 - 20.0 x ULN if baseline was normal; > 5.0 - 20.0 x ULN if baseline was abnormal)	Mandatory: permanently discontinue subject from all study drug treatments	<ol style="list-style-type: none">1. Monitor hepatic laboratory tests daily until returned to baseline values.2. Consider viral serology i.e. hepatitis A/B/C, CMV.3. Rule out other potential cause of liver injury such as con meds or alcohol4. Consult with hepatologist and perform liver biopsy to establish etiology of hepatic injury5. If after 2-3 days liver assessment shows worsening of laboratory tests consider to initiate treatment with steroids prednisone 1-2 mg/kg/day or i.v. equivalents.6. Add prophylactic antibiotics for opportunistic infections as appropriate7. When symptoms/liver function tests improve to Grade ≤1, taper steroids over at least 4 weeks.8. If serum transaminase levels or bilirubin do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given as per local treatment guidance. <p>Infliximab is not recommended due to its potential for hepatotoxicity</p>
Grade 4 (> 20.0 x ULN if baseline was normal; > 20.0 x ULN if baseline was abnormal)	Mandatory: permanently discontinue subject from all study drug treatments	As for Grade 3 toxicity above.

Hepatic Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Combined elevations of AST or ALT and Total Bilirubin ^{a, c}		
Any Grade		
<p>For subjects with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis ^b OR</p> <p>For subjects with elevated baseline AST or ALT or total bilirubin value: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with total bilirubin > 2 x baseline AND > 2.0 x ULN</p>	<p>Mandatory: permanently discontinue subject from all study drug treatments Patients with baseline grade 2 AST/ALT value (>3.0-5.0 ULN) may continue spartalizumab treatments</p>	<p>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 baseline or stabilization over 4 weeks</p>

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

^a "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

^b "Cholestasis" defined as: ALP elevation (> 2.0 x ULN and R value (ALT/ALP in x ULN) < 2.0) in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis

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

^d If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.

Table 6-11 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for Amylase and/or Lipase Elevation Related Adverse Events

Metabolic Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Symptomatic Amylase and/or Lipase elevation of any grade	Mandatory: permanently discontinue subject from all study drug treatments	<ul style="list-style-type: none"> • Test weekly (or more frequently) until \leq CTCAE Grade 2. • A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any \geq CTCAE Grade 3 result, to exclude disease progression or potential other liver or pancreatic disease.
Asymptomatic Amylase and/or Lipase elevation		
Grade 1 ($>$ ULN - 1.5 x ULN)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	Treat per local/institutional guidelines
Grade 2 ($>$ 1.5 - 2.0 x ULN)	Recommendation: interrupt study treatments until recovery to \leq Grade 1 or baseline	Treat per local/institutional guidelines
Grade 3 ($>$ 2.0 - 5.0 x ULN)	Mandatory: omit capmatinib and spartalizumab dose until resolved to \leq Grade 1, then: If resolved in \leq 14 days, resume capmatinib and spartalizumab treatment at the same dose level and schedule If resolved in $>$ 14 days, then restart capmatinib at \downarrow 1 dose level and spartalizumab at the normal dose level and schedule. If toxicity recurs permanently discontinue subject from all study drug treatments	Treat per local/institutional guidelines
Grade 4 ($>$ 5.0 x ULN)	Mandatory: permanently discontinue subject from all study drug treatments	Treat per local/institutional guidelines

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

Table 6-12 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for Cardiac Related Adverse Events

Cardiac Related Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Fridericia QT correction formula (QTcF) interval prolonged (NCI-CTCAE v5.0)		
Grade 1 (QTcF 450-480 ms)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	Treat per local/institutional guidelines
Grade 2 (QTcF 481-500 ms)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	Treat per local/institutional guidelines

Cardiac Related Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Grade 3 (QTcF \geq 501 ms on at least two separate ECGs)	<p>Mandatory: omit capmatinib and spartalizumab dose until resolved to \leq Grade 2, then:</p> <p>If resolved in \leq 7 days, resume capmatinib and spartalizumab treatment at the same dose level and schedule</p> <p>If resolved in $>$ 7 days, then restart capmatinib at \downarrow 1 dose level and spartalizumab at the normal dose level and schedule.</p> <p>If toxicity recurs permanently discontinue subject from all study drug treatments</p>	<ul style="list-style-type: none"> When QTcF \geq 501 ms (Grade 3), perform the following: <ul style="list-style-type: none"> Request an immediate manual read of the ECG. Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Review concomitant medication usage for the potential to inhibit CYP3A4/5 (Table 6-2) and/or to prolong the QT-interval (Table 6-4). Check compliance with correct dose and administration of capmatinib. Perform a repeat ECG within one hour of the first QTcF of \geq 501 ms. If QTcF remains \geq 501 ms, repeat ECG as clinically indicated, but at least once daily until the QTcF returns to $<$ 501 ms. Repeat ECGs 7 days and 14 days (and then every 21 days) after dose resumption for all subjects who had therapy interrupted due to QTcF \geq 501 ms. If QTcF of \geq 501 ms recurs, repeat ECGs as described above. <p>Notes:</p> <p>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.</p> <p>If the ECG report shows a QTcF \geq 501 msec (not previously documented on the site machine), contact the subject and instruct him/her to suspend capmatinib and return to repeat the ECG as soon as possible. The ECG reader should be called for a manual read of the repeat ECG immediately, and the above guidance followed.</p>
Grade 4 (QTcF \geq 501 or $>$ 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Mandatory: permanently discontinue subject from all study drug treatments	As for Grade 3 toxicity above

Cardiac Related Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Myocarditis grade ≥ 2 or other cardiac event grade ≥ 3	Mandatory: permanently discontinue subject from all study drug treatments	<ol style="list-style-type: none"> 1. Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg QD 2. Consult with cardiologist hospitalization as indicated

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

Table 6-13 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for Gastrointestinal Adverse Events

Gastrointestinal Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Pancreatitis		
Grade 2	Recommendation: see Table 6-11	<ul style="list-style-type: none"> • Evaluate for pancreatitis (clinical assessment, abdominal imaging and/or MRCP as appropriate) PDR001 may be continued in case of asymptomatic, isolated enzyme elevations without evidence for pancreatitis <p>Treat per local/institutional guidelines</p>
Grade ≥ 3	Mandatory: permanently discontinue subject from all study drug treatments	Treat per local/institutional guidelines
Diarrhea and/or Colitis ^a		
Grade 1 (despite appropriate anti-diarrheal medication)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	<p>Symptomatic treatment (loperamide, hydration, diet)</p> <ul style="list-style-type: none"> • Investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy for these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity). • The subject should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practice and the investigator's best judgment and may follow the "recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004).

Gastrointestinal Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Pancreatitis		
Grade 2 (despite maximal anti-diarrheal medication)	Mandatory: 1 st occurrence: Omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume treatment at same dose level and schedule 2 nd occurrence: If toxicity recurs, omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule.	1. Consult with GI specialist 2. Stool evaluation, imaging and endoscopy as clinically indicated 3. Symptomatic treatment (loperamide, hydration, diet) 4. 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) as per Section 6.5.3.1.1
Grade 3 (despite appropriate anti-diarrheal medication)	Mandatory: 1 st occurrence: Omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule. 2 nd occurrence: permanently discontinue subject from all study drug treatments	<ul style="list-style-type: none"> • Consider hospitalization; rule out bowel perforation and initiate IV hydration as needed • Consultation with GI specialist; consider endoscopy and biopsy • In addition to symptomatic treatment initial treatment with IV steroids (1 to 2 mg/kg/d of methylprednisolone or equivalent) • Consider antibiotics as appropriate • If no improvement in 2-3 days: consider initiating infliximab 5 mg/kg and continue steroids. (infliximab is contraindicated in patients with sepsis/perforation) • Slowly taper steroids once symptoms improve to Grade 1 (4 to 6 weeks) • If symptoms worsen during steroid reduction, re-escalate as needed followed by more prolonged taper and consider infliximab
Grade 4: Life-threatening consequences; urgent intervention indicated	Mandatory: permanently discontinue subject from all study drug treatments	Urgent hospitalization, supportive care and specialist consultation as outlined above in Grade 3
Vomiting		
Grade 1 (despite appropriate anti-emetics)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	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.

Gastrointestinal Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Pancreatitis		
Grade 2 (despite appropriate anti-emetics)	<p>Mandatory:</p> <p>1st occurrence: Omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume treatment at same dose level and schedule</p> <p>2nd occurrence: If toxicity recurs > Grade 2 omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule.</p>	As for Grade 1 toxicity above
Grade 3 (despite appropriate anti-emetics)	<p>Mandatory:</p> <p>1st occurrence: Omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume treatment at same dose level and schedule</p> <p>2nd occurrence: If toxicity recurs > Grade 2 omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule.</p>	Treat per local/institutional guidelines
Grade 4 (despite appropriate anti-emetics)	<p>Mandatory:</p> <p>1st occurrence: Omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume treatment at same dose level and schedule.</p> <p>2nd occurrence: If toxicity recurs > Grade 2 omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule.</p>	Treat per local/institutional guidelines
Nausea		
Grade 1 or 2 (despite appropriate anti-emetics)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	Treat per local/institutional guidelines

Gastrointestinal Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Pancreatitis		
Grade 3 (despite appropriate anti-emetics)	<p>Mandatory: 1st occurrence Omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then resume treatment at same dose level and schedule</p> <p>2nd occurrence: If toxicity recurs > Grade 2 omit capmatinib and spartalizumab dose until resolved to ≤ grade 1, then resume capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule.</p>	Treat per local/institutional guidelines

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

- ª Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea
 - Loperamide: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours;
 - Diarrhea > 24 hours: loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics.
 - Diarrhea > 48 hours: loperamide 2 mg every two hours; maximum 16 mg/day. Consider other second-line therapies for diarrhea (e.g: octreotide, oral diphenoxylate) and oral antibiotics

Table 6-14 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for Skin and Subcutaneous Tissue Adverse Events

Skin and Subcutaneous Tissue Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Rash/Photosensitivity		
Grade 1 Rash covering < 10% Body Surface Area (BSA)	<p>Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule</p>	<ol style="list-style-type: none"> 1. Monitor weekly 2. Initiate prophylactic and symptomatic treatment measures. 3. 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) 4. Reassess after 2 weeks.

Skin and Subcutaneous Tissue Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Grade 2 Rash covering 10-30% of BSA	Recommendation: consider dose interruption until tolerable or recovery to Grade ≤1 or baseline; once recovered resume treatment at the same dose and schedule Mandatory: in case of bullous dermatitis, acute generalized exanthematous pustulosis or Drug Rash with Eosinophilia and Systemic Symptoms, interrupt capmatinib and spartalizumab until recovery to Grade ≤1 or baseline.	1. Monitor weekly 2. 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 3. If symptoms persist or recur consider skin biopsy.
Grade 3 Rash covering more than 30% of BSA, despite skin toxicity therapy Other severe cutaneous adverse reactions Bullous dermatitis	Mandatory: Omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then, if resolved in ≤7 days resume treatment at same dose level and schedule. If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue subject from all study drug treatments For patients with severe cutaneous adverse reaction or bullous dermatitis, risk/benefit before resuming treatment should be carefully considered	1. Monitor daily 2. Consult with dermatologist and consider skin biopsy. 3. Initiate systemic steroids (1 mg/kg/d prednisone or IV equivalent); consider increasing if no improvement 4. High-potency topical steroids 5. Topical emollients, oral antihistamines as indicated 6. Consider GABA agonists or aprepitant in case of severe pruritus
Grade 4 Life-threatening	Mandatory: permanently discontinue subject from all study drug treatments	Urgent dermatologic consultation and additional measures as per local guidelines
Stevens-Johnson syndrome, toxic epidermal necrolysis	Mandatory: permanently discontinue subject from all study drug treatments	Hospitalization and urgent dermatology consultation Institute supportive care immediately as per local/institutional guidelines

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

Table 6-15 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for Respiratory, Thoracic and Mediastinal Adverse Events

Respiratory, Thoracic and Mediastinal Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
ILD and pneumonitis ^a	Mandatory: interrupt capmatinib and spartalizumab during diagnostic work up for ILD/ pneumonitis.	Subjects on combination therapy with capmatinib and spartalizumab should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. In addition, withhold capmatinib and spartalizumab for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for ILD/pneumonitis to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage.

Respiratory, Thoracic and Mediastinal Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Grade 1 Radiographic changes only-asymptomatic	<p>Mandatory: interrupt capmatinib and spartalizumab during diagnostic work up for ILD/ pneumonitis.</p> <p>In presence of a diagnosis of ILD/pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib and spartalizumab.</p> <p>Only in the absence of a diagnosis of ILD/pneumonitis, capmatinib and spartalizumab may be restarted at the same dose level and schedule. 2nd occurrence</p> <p>If it recurs after resumption of study drug it is mandatory to permanently discontinue both study drugs.</p>	<ol style="list-style-type: none"> 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
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental Activity daily living (ADL)	<p>Mandatory: interrupt capmatinib and spartalizumab during diagnostic work up for ILD/pneumonitis.</p> <p>In presence of a diagnosis of ILD/pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib and spartalizumab.</p> <p>Only in the absence of a diagnosis of ILD/pneumonitis, capmatinib and spartalizumab may be restarted at the same dose level and schedule 2nd occurrence</p> <p>If it recurs after resumption of study drug it is mandatory to permanently discontinue both study drugs.</p>	<ol style="list-style-type: none"> 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 ^b - if normal at baseline, repeat every 8 weeks 7. Bronchoscopy ^d 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).
Grade 3 or 4 Severe symptoms; limiting self care ADL; oxygen indicated or life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Mandatory: permanently discontinue subject from all study drug treatments	<ol style="list-style-type: none"> 1. CT scan (high-resolution with lung windows) 2. Clinical evaluation and laboratory work-up for infection 3. Commence oxygen therapy 4. Consult pulmonologist 5. Pulmonary function tests ^b -if < normal, repeat every 8 weeks until \geq normal 6. Bronchoscopy ^d with biopsy and/or BAL if possible 7. Treat with i.v. steroids ^c (methylprednisolone 125 mg) as indicated. When symptoms improve to \leq Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours). 8. If i.v. steroids followed by high dose oral steroids do not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication

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

^a Note: except if the subject is grade 2 at baseline in which case: it is \geq CTCAE grade 3.

^b 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 \leq 88% at rest on room air.

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

^d 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.

Table 6-16 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for Endocrine Adverse Events

Endocrine Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Grade 1 Asymptomatic , intervention not indicated (e.g. hyperthyroidism or hypothyroidism)	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	<ol style="list-style-type: none">1. If TSH $<0.5 \times$ LLN, or TSH $>2 \times$ ULN, or consistently out of range in two subsequent measurements, check free T4 at subsequent cycles as clinically indicated2. Consider endocrinologist consultation.3. If hypophysitis is suspected, consider pituitary gland imaging (MRIs with gadolinium and sellar cuts); evaluate hormone levels as clinically indicated4. Repeat labs in 1 to 3 weeks/MRI in 1 month if laboratory abnormalities persist but normal lab/pituitary scan

Endocrine Adverse Events		
Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
Grade 2 or 3 Symptomatic endocrinopathy (e.g., hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)	Mandatory: interrupt capmatinib and spartalizumab until diagnosis established and/or recovery to mild or no symptoms and controlled with hormone replacement therapy, then restart capmatinib and spartalizumab at the normal dose level and schedule. Recommended: hypothyroidism may be managed with replacement therapy without treatment interruption (unless life-threatening) Mandatory: permanently discontinue subject from all study treatments for life-threatening endocrinotherapies (i.e. hyperthyroidism, adrenal insufficiency, hypophysitis) or recurring severe/life-threatening events not controlled by hormone replacement therapy.	<ol style="list-style-type: none"> 1. Endocrine laboratory panel (TSH, T4, ACTH, FSH, LH, Prolactin, serum cortisol, aldosterone) and imaging (e.g. brain MRI) as clinically indicated 2. Consider endocrinologist consultation 3. If hypophysitis is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis) 4. Repeat labs in 1 to 3 weeks, MRI in 1 month if laboratory abnormalities persist but normal lab/pituitary scan 5. Rule out infection/sepsis and other alternative causes with appropriate cultures and imaging 6. Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day in case of severe hypophysitis or thyrotoxicosis. 7. Consider beta-blocker in case of severe hyperthyroidism 8. Replacement of appropriate hormones may be required as the steroid dose is tapered 9. Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis 10. Consider hospitalization (e.g. in case of severe adrenal insufficiency/crisis), fluid replacement, and other supportive measures as clinically indicated
Autoimmune diabetes (Grade 3 or symptomatic hyperglycemia) Autoimmune diabetes (Grade 4 hyperglycemia or life-threatening complications)	Mandatory: Omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1 or baseline, then resume treatment at same dose level and schedule. 2 nd occurrence: in case of recurring severe/life-threatening events not controlled by anti-glycemic therapy, permanently discontinue subject from all study drug treatment	<ol style="list-style-type: none"> 1. Initiate anti-glycemic therapy (i.e. insulin) as medically indicated 2. Monitor glucose levels regularly until metabolic control is achieved 3. Consider endocrinology consultation 4. Evaluate for ketoacidosis as medically indicated 5. Consider hospitalization (e.g. in case of ketoacidosis)

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

Table 6-17 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for General and Administration Site Adverse Events

General and Administration Site Adverse Events		
Grade	Dose Modification	Recommended Clinical Management
Fatigue/ Asthenia		
Grade 1 or 2	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	Treat per local/institutional guidelines
Grade 3	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1, then: If resolved in ≤7 days, resume capmatinib and spartalizumab treatment at the same dose level and schedule If resolved in >7 days, then restart capmatinib at ↓ 1 dose level and spartalizumab at the normal dose level and schedule.	Treat per local/institutional guidelines
Peripheral edema		
Grade 1 or 2	Recommendation: maintain capmatinib and spartalizumab at normal dose level and schedule	Consider conservative measures such as leg elevation, compression stockings and dietary salt modification as clinically indicated
Grade 3	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1 or baseline, then resume treatment at same dose level and schedule.	Intensify as above and treat per local/institutional guidelines
Grade 4	Mandatory: permanently discontinue subject from all study drug treatments	Intensify as above and treat per local/institutional guidelines
Other adverse events		
Grade 1 or 2	Recommendation: Continue capmatinib and spartalizumab at normal dose level and schedule For any intolerable Grade 2 (e.g.: limiting instrumental ADL), consider omitting the dose until resolved to ≤ grade 1, then ↓ capmatinib 1 dose level and continue spartalizumab at normal dose level and schedule	Treat per local/institutional guidelines
Grade 3	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 2, then resume treatment at same dose level and schedule.	Treat per local/institutional guidelines
Grade 4	Mandatory: permanently discontinue subject from all study drug treatments	Treat per local/institutional guidelines

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

Table 6-18 Dose Modifications of Capmatinib and Spartalizumab and Recommended Clinical Management for Other Potential Immune-Related Adverse Events of Special Interest including Cytokine Release Syndrome

Other Potential Immune-Related Adverse Events (e.g. Autoimmune neuropathy, demyelinating polyneuropathy, Guillain Barre, Myasthenia Gravis-like syndrome, encephalitis, non-infectious myocarditis, pericarditis, pancreatitis, grade 3 fatigue with rapid onset in absence of disease progression, etc.)	Grade (Worst Toxicity)	Dose Modification	Recommended Clinical Management
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Grade 1 (Mild, asymptomatic)	Recommendation: maintain capmatinib and spartalizumab at normal dose levels and schedules	Treat per local/institutional guidelines
Grade 2	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1 or baseline, then resume treatment at same dose level and schedule.	<ol style="list-style-type: none"> 1. Ensure adequate evaluation to confirm etiology or exclude other causes 2. Provide symptomatic treatment 3. Systemic corticosteroids may be indicated 4. Consider biopsy for confirmation of diagnosis 5. A specialist should be consulted
Grade 3	Mandatory: Omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1 or baseline May restart treatment at the same dose and schedule taking into account the risks and benefits; 2 nd occurrence: If toxicity recurs > Grade 2 permanently discontinue subject from all study drug treatments	<ol style="list-style-type: none"> 1. Ensure adequate evaluation to confirm etiology or exclude other causes 2. Provide symptomatic treatment 3. Initiate systemic corticosteroids (prednisone at a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate 4. Consider biopsy for confirmation of diagnosis 5. A specialist should be consulted
Grade 4	Mandatory: permanently discontinue subject from all study drug treatments	<ol style="list-style-type: none"> 1. Hospitalization and consult with specialist 2. Initiate systemic corticosteroids (prednisone a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate
Encephalitis or aseptic meningitis		
Any Grade	Mandatory: permanently discontinue subject from all study drug treatments	<ol style="list-style-type: none"> 1. Rule out infectious or other causes of moderate to severe neurologic deterioration 2. Consult with specialist. 3. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents.
Guillain-Barre Severe peripheral or autonomic neuropathy, or transverse myelitis		
Any Grade	Mandatory: permanently discontinue subject from all study drug treatments	<ol style="list-style-type: none"> 1. Rule out infectious or other causes of moderate to severe neurologic deterioration, and consult with specialist. 2. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents
Myasthenia gravis		
Grade 2	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1 or baseline, then resume treatment at same dose level and schedule.	<ol style="list-style-type: none"> 1. Consult with specialist 2. Consider pyridostigmine and systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d; other therapies as appropriate (e.g. i.v. immunoglobulin) 3. Hospitalization in case of severe cases
Grade 3 and 4	Mandatory: permanently discontinue subject from all study drug treatments	As Grade 2 toxicity above
Ocular events		
Grade 2	Mandatory: omit capmatinib and spartalizumab dose until resolved to ≤ Grade 1 or baseline, then resume treatment at same dose level and schedule.	Consult with ophthalmologist
Grade 3 and 4	Mandatory: permanently discontinue subject from all study drug treatments	As Grade 2 toxicity above

Infusion Related Reactions		
Grade 1	Recommendation: maintain spartalizumab at normal dose level and schedule.	<p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.</p> <p>Consider slowing infusion rate until recovery of symptoms</p>
Grade 2	Mandatory: Permanently discontinue of spartalizumab in case of recurring infusion related reaction despite adequate premedication and prolonged/slow infusion	<ol style="list-style-type: none"> 1. Stop Infusion 2. Additional appropriate medical therapy as per local institutional guidelines may include but is not limited to: <ul style="list-style-type: none"> • 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 with: <ul style="list-style-type: none"> • 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 or 4	Mandatory: permanently discontinue subject from all study drug treatments	<ol style="list-style-type: none"> 1. Stop Infusion 2. Additional medical therapy as per local institutional guidelines that may include: <ul style="list-style-type: none"> • 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.

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

6.5.3.1.1 Guidance for corticosteroids tapering for management of immune-related AEs

Consultation with disease-specific experts is recommended. Steroids should be tapered slowly and based on response/recovery of clinical symptoms. Consider complete tapering over a period of at least 4 weeks (sometime 6-8 weeks or longer) to prevent recurrent irAEs. Slower tapering or re-escalation of corticosteroids therapy may be needed if the adverse event is not showing improvement. Once corticosteroid tapering is achieved at a level of 10 mg of prednisone/day (or equivalent) or less, spartalizumab can be restarted as indicated in the dose modification tables.

6.5.3.2 Docetaxel dose modifications

Every attempt should be made to maintain the treatment dosing cycle schedule of every 21 days. For subjects who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted per the local approved label in order to keep the subject on treatment. For toxicities outlined below, docetaxel dose reduction will follow the local guidelines and approved product label. For each subject, a maximum of two dose modifications is allowed, after which the subject should be discontinued from treatment with docetaxel. If a subject misses more than two cycles of treatment, the subject should be discontinued from the study. However, if the Investigator and the Sponsor conclude that a subject, who has experienced a treatment interruption more than two cycles, could benefit from additional treatment, continuation may be allowed.

According to the manufacturer's label:

A new cycle of docetaxel will NOT be initiated if:

- Bilirubin > ULN, or
- AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN or
- Neutrophils < 1.5 x 10⁹/L or
- Platelets < 100 x 10⁹/L.

Subjects who are dosed initially at 75 mg/m² and who experience any of the following should have treatment withheld until resolution of the toxicity and then resume at the reduced dose as per [Table 6-18](#):

- Febrile neutropenia,
- Neutrophils < 500 cells/mm³ for more than one week,
- Severe or cumulative cutaneous reactions,
- Other Grade 3 or 4 non-hematological toxicities.

Subjects who develop \geq Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Dose changes must be recorded on the study treatment eCRF.

Table 6-19 Criteria for interruption and re-initiation of docetaxel treatment

Worst toxicity (CTCAE v5.0 Grade)	Dose Modifications for Docetaxel
HEMATOLOGICAL – Neutropenia (ANC)	
Nadir ANC <500/mm ³ and nadir platelets \geq 50,000/mm ³ .	Withhold until ANC is \geq 1500 cells/mm ³ and platelet count is \geq 100,000 cells/mm ³ , then resume at 75% of previous dose
Nadir platelets <50,000/mm ³ without bleeding regardless of nadir ANC	Withhold until ANC is \geq 1500 cells/mm ³ and platelet count is \geq 100,000 cells/mm ³ , then resume at 75% of previous dose
Nadir platelets <50,000/mm ³ with bleeding, regardless of nadir ANC	Withhold until ANC is \geq 1500 cells/mm ³ and platelet count is \geq 100,000 cells/mm ³ , then resume at 50% of previous dose
NONHEMATOLOGICAL (excluding neurotoxicity)	
Any Grade 3 or 4 toxicities except mucositis	Withhold until resolution to \leq the pre-therapy value, then resume at 75% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	Withhold until resolution to \leq the pre-therapy value, then resume at 75% of previous dose

Grade 3 or 4 mucositis	Withhold until resolution to ≤ to the pre-therapy value, then resume at 50% of previous dose
NEUROTOXICITY	
Grade 3, 4	Discontinue

6.5.4 Follow-up for toxicities

Capmatinib and spartalizumab

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for four weeks, and subsequently at approximately four week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologists, endocrinologists, dermatologists, psychiatrists etc. should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific study drug combination induced toxicities (hyperglycemia, diarrhea and skin toxicity) are provided in [Section 6.5.3](#). All subjects must be followed for adverse events and serious adverse events after discontinuation of spartalizumab and capmatinib. Please refer to [Section 9.2.1](#) for additional details.

The emergence of irAE may be anticipated based on the mechanism of action of immunomodulatory therapies.

Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the investigator to verify the immune-related nature of the AE and to exclude alternative explanations. Recommendations ([Section 6.5.3](#)) have been developed to assist investigators in assessing and managing the most frequently occurring irAEs.

Subjects 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. If cytokine release syndrome is suspected, the assessments outlined in [Table 6-17](#) must be performed.

[Table 6-8](#), [Table 6-9](#), [Table 6-10](#), [Table 6-11](#), [Table 6-12](#), [Table 6-13](#), [Table 6-14](#), [Table 6-15](#), [Table 6-16](#), [Table 6-17](#), [Table 6-18](#) outline the follow-up evaluations recommended for selected toxicities.

Docetaxel

Safety follow-up for toxicities related to docetaxel should follow the local guidelines and approved product label. All subjects must be followed for adverse events and serious adverse events after discontinuation of docetaxel. Please refer to [Section 9.2.1](#) for additional details.

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

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

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

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation $> 2.0 \times$ 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 the absence of cholestasis, these subjects should be immediately discontinued from study treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. PK samples should be obtained, as close as possible to last dose of, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Every time the study treatment is to be administered, IRT needs to be accessed (please refer to the IRT manual). The date and time of study treatment administration during the study and any deviations from the protocol treatment schedule will be captured on the appropriate study treatment dispensing form. The investigator must promote compliance by instructing the 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.

For treatment with spartalizumab or with docetaxel: exposure to the study treatment will be based on the number of injections administered. Compliance with the study treatment will be assessed by the Clinical Research Associate (CRA) at each visit using vial counts and information provided by the pharmacist or by the investigator. All study treatment dispensed and returned must be recorded in a drug accountability log.

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

Pharmacokinetic parameters will be determined in all subjects treated with capmatinib and spartalizumab combination, as detailed in pharmacokinetics section. Please refer to [Section 8.5.2](#).

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

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

Capmatinib

The investigator or responsible site personnel must instruct the subject or caregiver to take the study treatment as per protocol. Study treatment will be dispensed to the subject by authorized site personnel only. All dosages prescribed to the subject and all dose changes during the study must be recorded on the study treatment eCRF.

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

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

Spartalizumab

Study treatment will be dispensed and administered to the subject by authorized site personnel only. All dosages prescribed to the subject and all dose changes during the study must be recorded on the study treatment eCRF. A unique medication number is printed on the study medication label.

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

Spartalizumab will be administered intravenously as a 30 minute 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. Clinical monitoring during and post infusion should be performed according to local practice and institutional guidelines, and as outlined in [Section 6.7.2.2](#). Further instructions for the preparation and dispensation of spartalizumab are described in the [Study Pharmacy Manual].

Docetaxel

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

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 and in the [capmatinib Investigator's Brochure] and [spartalizumab Investigator's Brochure]. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organisation Quality Assurance.

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

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug

accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

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

Table 6-20 Dose and treatment schedule

Investigational / Control Drug	Dose	Frequency and/or Regimen
Capmatinib (INC280) 150 mg or 200 mg	400 mg orally (2 x 200 mg or 2 x 150 mg [if dose is reduced to 300 mg BID] or 1 x 200 mg [if dose is reduced to 200 mg BID], if applicable)	Twice daily (28 day cycles)
Spartalizumab (PDR001) 100 mg	400 mg i.v. (4 x 100 mg vials)	Once every 28 days
Docetaxel (as per local product available)	75 mg/m ² i.v. infusion per product label and local guidelines (as per standard of care)	Once every 21 days

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.

- Including days of PK sampling, subjects should take 400 mg of capmatinib tablets twice daily (BID) at approximately the same time each day starting at 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 1 tablet every 2 minutes).
- Subjects should be instructed to swallow the tablets whole and not to chew them.
- Capmatinib can be administered with or without food. The morning and the evening doses should be taken 12 (\pm 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 infusion along with its pre-medication (if pre-medication is necessary). The sequence will allow consistent time of daily dosing for capmatinib. A minimum of 1 hour must pass from the time of capmatinib (morning dose) administration to the administration of spartalizumab.

- On days when PK blood samples are to be collected, subjects will be instructed to hold their dose until arrival at the study center. Capmatinib will be administered at the site in the morning prior to the post-dose PK sample blood draws supervised by a member of the research team. The pre-dose PK samples will be taken right before capmatinib administration. The exact time of drug administration should be recorded in the appropriate eCRF. If a subject vomits within 4 hours of capmatinib dosing, the time of vomiting should be recorded on the eCRF.
- 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).

The investigator should instruct the subject to take capmatinib exactly as prescribed. All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the study treatment eCRF.

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

6.7.2.2 Spatalizumab

Spatializumab will be supplied in a vial as liquid solution for infusion. Spatializumab (liquid) will be diluted in dextrose 5% in water (D5W). Due to incompatibility, 0.9% sodium chloride must not be used.

The dose of spatalizumab is 400 mg every 4 weeks given as a 30 minute infusion (up to 2 hours, if clinically indicated). A dose may be delayed by up to seven days. If a dose cannot be administered within the planned window then the dose on that cycle should be skipped. The dose may be interrupted for up to 12 weeks. The safety assessments (as per [Table 8-2](#)) should be performed according to the actual day of infusion.

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 spatalizumab infusions. The same may apply for the subsequent spatalizumab infusions if medically indicated. Subjects should be further provided instructions to notify study personnel if symptoms of infusion reaction occur after any spatalizumab infusion.

On days when PK blood samples are to be collected, study visits should be scheduled in the morning so that a predose PK blood sample can be collected. The exact time of drug administration should be recorded in the appropriate eCRF.

6.7.2.3 Docetaxel

Chemotherapy administration (including related steroid pre-medication schemes) should follow local guidelines as per standard of care and product labels.

For docetaxel, a complete treatment cycle is defined as an infusion with docetaxel (per local guidelines as per standard of care and product labels) during a 21 day cycle.

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

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

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

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

Subjects will be asked to complete an optional questionnaire to provide feedback on their clinical trial experience. (Please refer to [Section 8.5.1](#)).

8 Visit schedule and assessments

Assessment schedules [Table 8-2](#) (capmatinib and spartalizumab treated subjects [including run-in]) and [Table 8-3](#) (docetaxel treated subjects) list all of the assessments and indicate with an “X” or “S” the visits when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Written informed consent must be obtained before any study specific assessments are performed. Main screening evaluations and baseline radiological tumor assessments should be performed within 28 days of treatment start. All visits are to be scheduled according to the appropriate number of calendar days from Cycle 1 Day 1 of study drug administration. Visit windows per [Table 8-1](#) are allowed.

Table 8-1 Allowable window for subject assessments

Visit name	Window allowed
Screening	-28 days from 1 st dose of study drug
C1D1	Within 3 days after enrollment (part 1) or randomization (part 2)
C1D15	± 1 day
C2D1	± 3 days
C3D1	± 3 days
C3D4	± 1 day (applicable only to intensive PK group)
C3D8	± 1 day (applicable only to intensive PK group)
C3D15	± 1 day
C4D1	± 3 days
Day 1 visit of all subsequent cycles	± 3 days
Imaging evaluations	± 7 days
EOT	≤ 7 days after stopping study treatment
30 day safety follow-up visit	+ 7 days
60, 90, 120 day follow-up phone call/onsite visit	± 14 days
150 day follow-up phone call/onsite visit	+ 14 days
Survival follow-up	± 14 days

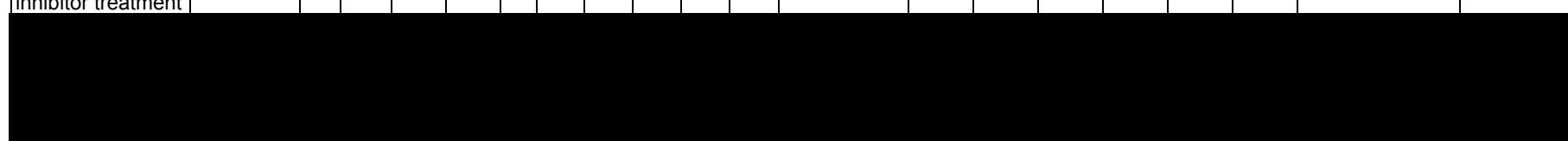
Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol. If a given visit is out of window, the next visit should be performed with reference to the day of first dose in order to get the subject back on schedule. If an off-schedule imaging assessment is performed, subsequent imaging assessments should be performed in accordance with the original imaging schedule. 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, during which 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.

Table 8-2 Assessment Schedule, Run-in and Arm 1 (capmatinib and spartalizumab combination) - length of a cycle is 28 days

Period	Screening	Treatment												Safety Follow-Up (FUP)				
Visit Name	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	D4	D8	D15	D1	D1	D1	D1	-	-	-	-	-	
Concomitant medications	X (from 28 days prior to starting treatment until 150 day safety follow-up or start of new antineoplastic medication (ANP), whichever is sooner. If new ANP is started, only medications relative to suspected AEs/SAEs that are reported should be collected)																	
IRT registration		X ¹		S ²	S ²				S ²	S ²	S ²	S ²	S ³					
Physical Examination ⁴	S	S (if clinically indicated)																
Targeted Physical Examination		S		S	S				S	S	S	S	S					
Body Height	X																	
Body 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	X				
Chemistry	X	X	X	X	X				X	X	X	X	X	X				
Coagulation Panel	X	X (if clinically indicated)																
Serum Pregnancy test	S (within 72h prior to first dose)												S	S			S	
Urine Pregnancy test				S	S				S	S	S	S		S	S	S		
Urinalysis	S	S (if clinically indicated)																
Thyroid stimulating hormone	X			X	X				X	X	X	X	X	X				

Period	Screening	Treatment												Safety Follow-Up (FUP)				
Visit Name	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	D4	D8	D15	D1	D1	D1	D1	-	-	-	-	every 8 weeks until PD	every 8 weeks
Thyroid Panel – Free T3 and Free T4	X			X (only if TSH is abnormal)														
Hepatitis screen	X	X (if clinically indicated)																
HIV testing if locally required	S																	
Cytokines	X	X (anytime when a suspected cytokine release syndrome occurs, immediately after the AE, and one week after occurrence of the AE)																
CT/MRI of chest and abdomen (with intravenous contrast enhancement)	X			X				X		X ⁵	X ⁶						X ⁵	
CT/MRI of pelvis and brain	X			X ⁷				X ⁷		X ⁷	X ⁷						X ⁷	
Whole body bone scan	X	X (if clinically indicated)																
Localized bone scan (CT, MRI or X-ray)	X ⁸			X ⁷				X ⁷		X ⁷	X ⁷						X ⁷	
CT/MRI of other metastatic sites	X (if clinically indicated)			X ⁷				X ⁷		X ⁷	X ⁷						X ⁷	
Photography for any skin lesion	X			X ⁷				X ⁷		X ⁷	X ⁷						X ⁷	

Period	Screening	Treatment												Safety Follow-Up (FUP)					Efficacy FUP (until PD)	Survival FUP
Visit Name	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	D4	D8	D15	D1	D1	D1	D1	D1	-	-	-	-	-	every 8 weeks until PD	every 8 weeks
Electrocardiogram (ECG)	X	X	X (only Run-in)	X (only Run-in)	X (only Run-in)				X					X (every subsequent third cycle)	X					
Adverse Events	X (suspected AEs up to Day 150; non-suspected AEs up to Day 150 or start of new post treatment anti-neoplastic medication, whichever is sooner)																			
Serious Adverse Events	X (suspected SAEs up to Day 150 and beyond; non-suspected SAEs up to Day 150 or start of new post treatment anti-neoplastic medication, whichever is sooner)																X (SAEs related to study treatment)			
Newly obtained tumor biopsy (preferred) or archival tumor sample		X																		
Optional and if not already provided: additional tissue material or block collected after disease progression on PD-(L)1 checkpoint inhibitor treatment		X																		



Period	Screening	Treatment												Safety Follow-Up (FUP)					
Visit Name	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	D4	D8	D15	D1	D1	D1	D1	-	-	-	-	-	every 8 weeks until PD	every 8 weeks
Blood for circulating tumor DNA		X		X	X					X	X (every subsequent third cycle)	X (at the time of first disease progression prior to the initiation of new anti-cancer therapies)							
Blood for cytokine analysis		X	X	X	X			X				X (at the time of first disease progression prior to the initiation of new anti-cancer therapies)							
Blood for gene expression		X	X	X								X (at the time of first disease progression prior to the initiation of new anti-cancer therapies)							
Trial Feedback Questionnaire		S						S				S							
PK blood collection - sparse		X	X	X	X			X	X		X	X (at C8, C10, C12 and every 6 cycles thereafter)	X	X			X ⁹		

Table 8-3 Assessment Schedule, Arm 2 (Docetaxel) - length of a cycle is 21 days

Period	Screening	Treatment							Safety FUP	Efficacy FUP	Survival FUP
Visit Name	Screening	C1	C2	C3	C4	Subsequent cycles	EOT	30 day	-	-	-
Days	-28 to -1	D1	D15	D1	D1	D15	D1	D1	-	every 8 weeks until PD	every 8 weeks

8.1 Screening

All subjects must provide a signed main ICF prior to performing any screening procedures to determine subject eligibility. Subjects will be evaluated against all study inclusion and exclusion criteria. Baseline evaluations must be performed within 4 weeks (≤ 28 days) prior to the first dose of study drug.

After signing the study ICF, the screening assessments will be done within 1 to 28 days prior to the first dose of study drug. Laboratory parameters may be retested within the 28 day screening window (Day -28 to Day -1) period for an individual subject if such parameters meet an exclusion criterion when initially tested. Laboratory assessments performed as part of the screening evaluations will not be required to be repeated prior to dosing (except serum pregnancy test if not done within 72 hours prior to treatment start, and hematology/chemistry if not done within 7 days prior to treatment start) unless deemed clinically necessary by the investigator and/or required as per local institutional policies. The cardiac eligibility criteria should be assessed with the ECG report. Imaging assessments will be performed at screening between Day -28 and Day -1. Imaging assessments already completed during the regular work-up of the subject within 28 days prior to start of treatment, including before signing the main study ICF can be considered as the baseline images for this study. Any imaging assessments obtained after first dose of study treatment cannot be considered baseline images. For details on screening assessments, refer to [Table 8-2](#) and [Table 8-3](#).

A new ICF will need to be signed if the investigator chooses to re-screen the subject after a subject has screen failed. A new subject number will be assigned to the patient. The rescreen form will have to be completed in the eCRF and in IRT to provide the original subject number. All required screening activities must be performed when the subject is re-screened for participation in the study. An individual subject may only be re-screened once for the study. Once the number of subjects screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the subjects who screen failed will not be permitted to re-screen.

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

8.1.1 Eligibility screening

When all screening procedures are completed and once the subject's eligibility has been checked and confirmed (i.e., all inclusion/exclusion criteria have been verified), the key eligibility criteria checklist will be completed prior to the first dose of study drug in the IRT system by the investigator or designee. The eligibility check will be embedded in the IRT system. For the randomized part of the study, allocation to one of the two study arms will also be registered via IRT.

Please refer to [Section 6.3.2](#) and as well as comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

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

8.2 Subject demographics/other baseline characteristics

Data to be collected on subject characteristics at screening include:

- Demography (age, gender, race and ethnicity, or as allowed by local regulations)
- Other background or relevant medical history (including smoking history)/ (serious) adverse events
- Any additional treatment received after the PD-(L)1 inhibitor and enrollment in the current study and response to the received additional treatment
- Cancer characteristics including diagnosis, history, extent of cancer, EGFR and ALK mutation status, prior antineoplastic therapies (medications, radiation, surgeries), and date of progression prior to study entry
- Tumor imaging assessments
- Other assessments to be completed for the purpose of determining eligibility (ECOG performance status, complete physical examination, vital signs, hematology, blood chemistry, coagulation studies, cytokines, thyroid panel, TSH, urinalysis, HBV and HCV status, HIV testing where locally required [only recorded in source documentation], serum pregnancy test for women of child-bearing potential [only recorded in source documentation], and 12-Lead ECG)
- Prior and current concomitant medications and surgical and medical procedures
- [REDACTED]

Data to be collected on C1D1 pre-dose include:

- [REDACTED]
- 12-Lead ECG (pre-dose in run-in subjects only)
- PK/IG (for capmatinib and spartalizumab combination subjects only)

8.3 Efficacy

8.3.1 Efficacy Assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.2 based on RECIST 1.1 (available in [Section 16.1](#)) ([Eisenhauer et al 2009](#)), except in the situation of treatment beyond initial disease progression as per RECIST 1.1

[REDACTED]

[REDACTED]

Subjects should have at least one documented measurable lesion at study entry as per RECIST 1.1. The imaging assessment collection plan is presented in [Table 8-4](#). Information regarding prior interventions (e.g. radiotherapy), pre-existing radiographic findings that mimic metastatic disease at screening and prior interventions should be entered in the clinical database. Information regarding cytology results should also be entered in the clinical database.

Table 8-4 Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
CT/MRI of the chest and abdomen (with intravenous contrast enhancement)	Mandated	Every 8 weeks starting at Cycle 3 until 12 months; then every 12 weeks until PD per RECIST 1.1 (and at end of treatment if not done within 28 days)*
CT/MRI of pelvis (with intravenous contrast enhancement)	Mandated	Only if lesions were documented at screening; follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated
CT/MRI of the brain	Mandated	Only if lesions were documented at screening; follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated
Whole body bone scan	Mandated	Only if clinically indicated
Localized bone CT, MRI or x-ray	Mandated for any lesions identified on the whole body bone scan that are not visible on the CT/MRI of the chest, abdomen and pelvis	Only if lesions were documented at screening; follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated
CT or MRI of other metastatic sites (e.g., neck)	If clinically indicated	Only if lesions were documented at screening, follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated
Color photography (with scale/ruler)	Mandated for any skin lesions present	Only if lesions were documented at screening, follow the same schedule as CT/MRI of the chest and abdomen, or if clinically indicated

Baseline imaging assessments

Imaging assessments will be performed at screening within 28 days prior to first dose of study treatment.

Any imaging assessments already completed during the regular work-up of the subject within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after first dose of study treatment cannot be considered baseline images. Please refer to [Table 8-4](#) for a list of imaging assessments required at baseline.

The following assessments are required at screening:

- CT/MRI of the chest and abdomen
- CT/MRI of the pelvis

- CT/MRI of the brain
- Whole body bone scan
- Localized bone CT, MRI or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI
- CT or MRI of other metastatic sites (e.g., neck), if clinically indicated
- Color photography with a scale/ruler for any skin lesions present

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

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

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

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

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

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

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

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

Post-baseline imaging assessments

Imaging assessments as described in [Table 8-4](#) should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see [Table 8-1](#)) and will be performed every 8 weeks (+/- 7 days) for the first 12 months and then every 12 weeks until study discontinuation criteria are met per [Section 9.1](#). Each lesion that is measured at baseline must be measured by the same method and, when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. The same is true

for any new lesions that occur after start of treatment. They should be imaged using the same modality at each subsequent time point. Imaging assessments should be scheduled using the date of first dose of study treatment as the reference date (not the date of the previous tumor assessment), and should be respected regardless of whether study treatment is temporarily withheld or unscheduled assessments performed. If an unscheduled imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, as necessary.

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. Please see [Section 6.1.5.1](#) for additional information.

Efficacy follow-up

For subjects who discontinue treatment for reasons other than initial disease progression as per RECIST 1.1, tumor assessments must continue to be performed as outlined in [Table 8-2](#) and [Table 8-3](#). Please refer to [Section 9.2.2](#) for additional information.

Overall survival

All Subjects will enter the survival follow-up period once they complete the safety follow-up and efficacy follow-up after treatment discontinuation (whichever is longer). Survival status will be collected every 8 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. Additional survival assessments may be performed outside the 8 weeks follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs. Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs. Information on the therapies received for NSCLC, if any, after study treatment has been completed will be collected.

8.3.2 Appropriateness of efficacy assessments

Tumor response as specified in [Section 8.3.1](#) will be assessed locally according to the Novartis guideline version 3.2 based on RECIST 1.1 ([Section 16.1](#)) ([Eisenhauer et al 2009](#)) [REDACTED]

[REDACTED] Tumor assessments every 8-12 weeks are consistent with the standard clinical practice. National Comprehensive Cancer Network (NCCN) guidelines for NSCLC recommend response assessment every 6-12 weeks. In patients with NSCLC previously treated with platinum chemotherapy, the median PFS is approximately 4 months or 16 weeks.

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 10.1.1](#).

Table 8-5 Physical Assessments

Assessments	Specification
Physical examination	<p>Significant findings that were present prior to the signing of informed consent must be included as medical history on the subject's eCRF. Significant new findings that begin or worsen after informed consent must be recorded as an adverse event on the appropriate eCRF.</p> <p>Physical examination At screening, a complete physical examination will be performed including the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological systems. More frequent examinations may be performed at the discretion of the investigator and if medically indicated. Information about the physical examination must be present in the source documentation.</p> <p>Targeted physical examination A targeted physical exam will be performed at all visits as indicated in Table 8-2 and Table 8-3 during treatment except where a complete physical examination is required (see above). It will include at least the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). If indicated based on symptoms, additional exams will be performed. Information for all physical examinations must be included in the source documentation at the study site and additionally reported in appropriate eCRF pages for blood pressure (SBP and DBP), vital signs, height and weight.</p>
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature. They will be measured at screening and at subsequent time points as specified in Table 8-2 and Table 8-3 .
Height and weight	Height will be measured at screening. Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-2 and Table 8-3 .
Performance status	The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale as specified in Table 8-6 following the schedule given in Table 8-2 and Table 8-3 .

Table 8-6 ECOG Performance Status

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

8.4.1 Laboratory evaluations

Central laboratories will be used for the analysis of scheduled hematology, biochemistry and other blood specimens collected as part of safety monitoring (as detailed in [Table 8-2](#) and [Table 8-3](#)).

Table 8-3). 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.

Dipstick urinalysis (macroscopic panel) will be performed at the site. In the event of any out of range parameters, a local laboratory microscopic panel will be performed.

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

The 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. Visit windows are allowed for all visits. Please refer to [Table 8-1](#).

If at any time a subject has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the normal ranges and units for this laboratory and the laboratory certification, when possible. The investigator is responsible for reviewing all laboratory reports for subjects in the study and evaluating any abnormalities for clinical significance.

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

- A treatment decision was made based on the local results, or
- There are no concomitant central results available, or
- Local lab results document an AE not reported by the central lab, or
- Local lab results document an AE where the severity is worse than the one reported by the central lab.

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 8-7 Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Hematocrit, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred, %s are acceptable))
Chemistry	Albumin, Alkaline Phosphatase, ALT, Amylase, AST, Calcium, Creatinine, Creatinine Clearance, Total Bilirubin, Direct Bilirubin (only if total bilirubin is \geq grade 2), Indirect Bilirubin, Prothrombin Time, GGT, Lipase, Magnesium, Sodium, Potassium, fasting Glucose (non- fasting glucose allowed post-baseline), Blood Urea Nitrogen (BUN) or Urea, Bicarbonate, Chloride and Uric Acid: at screening and thereafter as clinically indicated, Lactate dehydrogenase (LDH), Phosphorus, Creatine kinase, Total Cholesterol
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	Activated Partial Thromboplastin Time (aPTT), International Normalised Ratio (INR)
Thyroid	TSH (Thyroid Stimulation Hormone), Free T3 and Free T4. At the subsequent visits as indicated in Table 8-2 : TSH only. If TSH is abnormal, central lab will test Free T3 and Free T4
Hepatitis marker	HBV DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR
Safety cytokines (for cytokine release syndrome)	IFN- γ , IL-6, IL-1, TNF- α
Pregnancy Test	A serum pregnancy test must be performed at screening (at the local laboratory) within \leq 72 hours before first dose of study treatment, then the schedule of serum and urine pregnancy tests should be performed as indicated in Section 8.4.3 . If local requirements dictate otherwise, local regulations should be followed.

8.4.1.1 Hematology

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

Laboratory assessment done \leq 7 days of first dose of study treatment are permitted to be used as Cycle 1 Day 1 labs and do not need to be repeated.

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

8.4.1.2 Clinical chemistry

Clinical chemistry tests are to be performed according to the visit schedule outlined in [Table 8-2](#) and [Table 8-3](#). For details of the biochemistry panel see [Table 8-7](#). Biochemistry should be assessed on the actual scheduled day, even if study drug is being withheld.

Laboratory assessment done \leq 7 days of first dose of study treatment are permitted to be used as Cycle 1 Day 1 labs and do not need to be repeated.

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

8.4.1.3 Urinalysis

Urinalysis is to be performed according to the visit schedules outlined in [Table 8-2](#) and [Table 8-3](#). For details of the urinalysis panel see [Table 8-7](#).

8.4.1.4 Coagulation

INR and aPTT are to be performed according to the visit schedule outlined in [Table 8-2](#) and [Table 8-3](#).

8.4.1.5 Thyroid function

Thyroid function will be performed at:

- Screening/baseline: TSH, Free T3, Free T4
- Day 1 of subsequent cycles, EOT, 30 day safety follow-up: TSH
 - If TSH is abnormal, central lab will test Free T3 and Free T4.

8.4.1.6 Hepatitis marker

Hepatitis panels outlined in [Table 8-7](#) will be performed at screening and as clinically indicated while on study treatment as per the assessment schedule in [Table 8-2](#) and [Table 8-3](#). HBV DNA serology (including HBV DNA, HBsAg, HBsAb, HBcAb) and HCV RNA-PCR test will be performed at baseline screening (\leq 28 days prior to start of study treatment) and as clinically indicated (hepatitis markers should be evaluated for precautionary safety monitoring of viral reactivation 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
- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core antibody (HBcAb)
- Hepatitis B surface antibody (HBsAb)

Hepatitis C:

At screening, all subjects will be tested for quantitative HCV RNA-PCR. After start of the study treatment and until 30 day safety follow-up, testing for HBV and HCV should be performed if clinically indicated. (e.g., criteria of hepatitis reactivation, rule out viral causality in case of DILI).

8.4.1.7 Cytokine analysis

Samples for safety cytokine panel at screening will be stored below -70°C and analyzed only if post-screening samples are received. Cytokine panel is to be performed according to the visit schedules outlined in [Table 8-2](#).

8.4.2 Electrocardiogram (ECG)

ECGs should be recorded after the subject has been resting for 10 minutes in the supine position to ensure a stable baseline, followed by the first ECG recording over the next 5 minutes. Triplicate ECGs should be performed approximately 2 minutes apart prior to the time point indicated in [Table 8-8](#), [Table 8-9](#), and [Table 8-10](#) below. ECGs should be performed within 20 minutes prior to the collection of PK sample where applicable. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

The Fridericia QT correction formula (QTcF) should be used for clinical decisions. The QTcF values from the triplicate ECGs will be averaged for each time point.

Triplicate ECGs for assessment will be collected at certain visits and whenever abnormality occurs at any time. Clinically significant ECG findings must be recorded as adverse events.

Table 8-8 ECG collection plan Part 1: Run-in

Cycle	Day	Time	ECG Type
Screening		Anytime	12 Lead, triplicate
1	1	Pre-dose	12 Lead, triplicate
1	15	Pre-dose	12 Lead, triplicate
2	1	1h post spartalizumab end of infusion	12 Lead, triplicate
3	1	Pre-dose and 1h post spartalizumab end of infusion	12 Lead, triplicate
4	1	Anytime	12 Lead, triplicate
Every subsequent third cycle		Anytime	12 Lead, triplicate
End of treatment		Anytime	12 Lead, triplicate
Unscheduled ECG		Anytime if clinically indicated	12 Lead, triplicate

Table 8-9 ECG collection plan Part 2: Randomized to Arm 1: capmatinib and spartalizumab combination

Cycle	Day	Time	ECG Type
Screening		Anytime	12 Lead, triplicate
1	1	Anytime	12 Lead, triplicate
4	1	Anytime	12 Lead, triplicate
Every subsequent third cycle		Anytime	12 Lead, triplicate
End of treatment		Anytime	12 Lead, triplicate
Unscheduled ECG		Anytime if clinically indicated	12 Lead, triplicate

Table 8-10 ECG collection plan Part 2: Randomized to Arm 2: docetaxel

Cycle	Day	Time	ECG Type
Screening		Anytime	12 Lead, triplicate

Cycle	Day	Time	ECG Type
1	1	Anytime	12 Lead, triplicate
4	1	Anytime	12 Lead, triplicate
Every subsequent third cycle		Anytime	12 Lead, triplicate
End of treatment		Anytime	12 Lead, triplicate
Unscheduled ECG		Anytime if clinically indicated	12 Lead, triplicate

Note: An unscheduled ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page.

Each ECG tracing should be labeled with the study number, subject initials (where regulations permit), subject number and date and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening should be reported on the medical history eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the adverse events eCRF page.

8.4.3 Pregnancy and assessments of fertility

All sexually active males and sexually active females of child-bearing potential are required to use highly effective methods of contraception during the study and for the follow-up time period as specified in [Section 5.2](#). For a definition of highly effective contraception, assessment of fertility (males and females), and the definition of post-menopausal, please refer to [Section 5.2](#).

All women of child-bearing potential will have a serum pregnancy test within 72 hours prior to the first dose of study treatment. hCG may also be considered a tumor marker, therefore if hCG levels are detected, another blood sample at least 4 days later must be taken to assess the kinetics of the increase, and a transvaginal ultrasound must be performed to rule out pregnancy.

Women treated with capmatinib and spartalizumab combination

Monthly urine pregnancy tests will then be required to be performed on Day 1 of every cycle beginning with Cycle 2, followed by serum pregnancy test at the end of treatment visit, 30 day and 150 day safety follow-up visit. During the follow-up period after the 30 day safety follow-up visit through the 120 day safety follow-up telephone call, women of child-bearing potential will perform at-home urine pregnancy testing every 30 days using kits provided. Every effort must be made for the women of child-bearing potential to return to the site for the final pregnancy test. However, if the subject is unable to return then the subject will administer the urine pregnancy test at home using the kit provided. For all pregnancy tests performed at home, the site personnel will follow-up with the subject via telephone call to collect the date and the test results and document the information in the subject's source documents. If the subject returns to the site for the serum pregnancy test at the 150 day safety follow-up, the results must be documented in the subject's source documents.

Women of child-bearing potential will be instructed to contact the site immediately at any time during the study (on-treatment or during follow-up) should they have a positive pregnancy test. In case of positive urine pregnancy testing, additional testing must be performed to confirm the pregnancy, and, if confirmed, follow the reporting requirements as described in [Section 10.1.4](#).

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

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

Women treated with docetaxel

Monthly urine pregnancy tests will then be required to be performed on Day 1 of every cycle beginning with Cycle 2, followed by a serum pregnancy test at the end of treatment visit and at the 30 day safety follow-up visit. Every effort must be made for the women of child-bearing potential to return to the site for the final pregnancy test.

Women of child-bearing potential will be instructed to contact the site immediately at any time during the study (on-treatment or during follow-up) should they have a positive pregnancy test. In case of positive urine pregnancy testing, additional testing must be performed to confirm the pregnancy, and, if confirmed, follow reporting requirements as described in [Section 10.1.4](#). A positive pregnancy test requires immediate discontinuation of study treatment. If a positive pregnancy test is performed in between study visits, the subject must immediately notify the investigator. Male subjects must notify the investigator in case their partner is confirmed with positive pregnancy test results during the treatment period. See [Section 10.1.4](#) for pregnancy reporting.

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

Assessments of fertility

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

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

8.4.4 Appropriateness of safety measurements

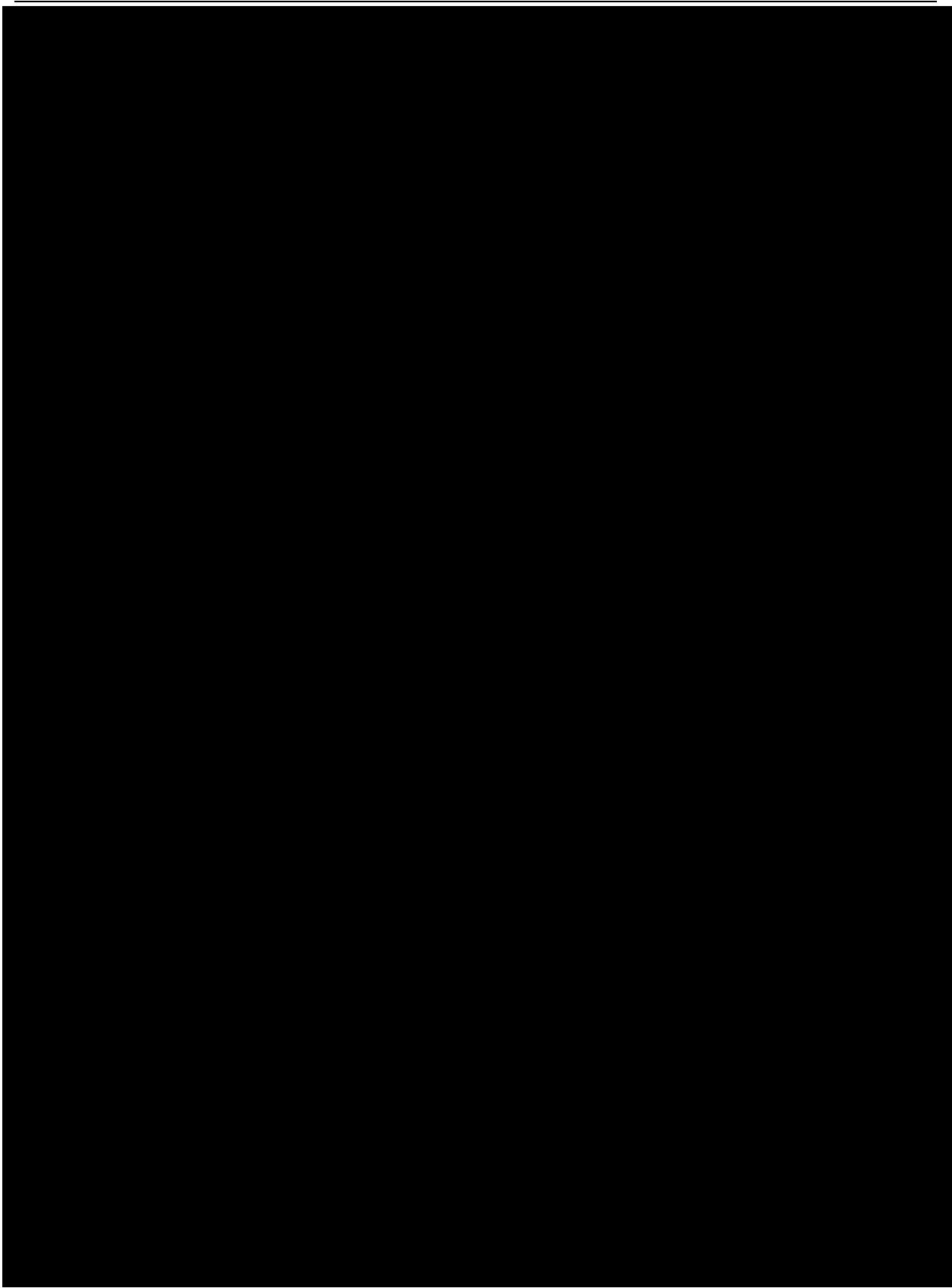
The safety assessments selected are standard for this indication/subject population.

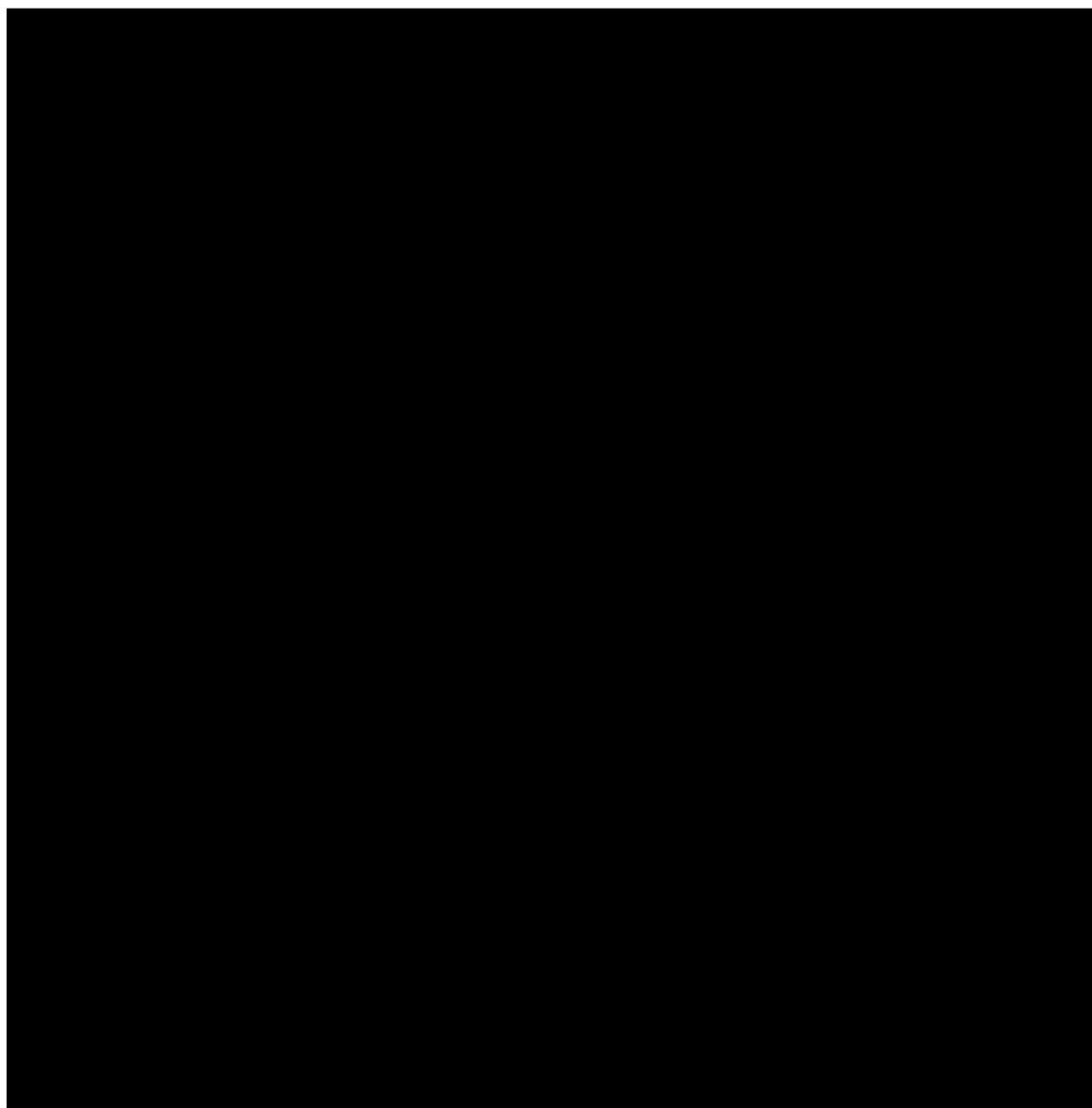
8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Trial Feedback Questionnaire (TFQ)

This trial will include an anonymized questionnaire, the "Trial Feedback Questionnaire," for subjects to provide feedback on their clinical trial experience. Individual subject level responses will not be reviewed by investigators. Responses may be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the subject's disease, symptoms, treatment effect or adverse events, and, therefore, will not be trial data.





8.5.2 Pharmacokinetics

Blood samples will be collected from all subjects in run-in and in arm 1 for the analysis of plasma capmatinib and its major metabolite CMN288, and serum spartalizumab concentrations, as well as for IG analysis.



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 and CMN288 analysis in plasma. Another 2 mL of blood will be collected for spartalizumab analysis in serum and 3.5 mL will be collected for IG analysis in serum. For time points when spartalizumab PK and IG are to be measured, a single blood sample will be collected for both IG and 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 and IG 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 and CMN288 are outlined in [Table 8-11](#) and [Table 8-12](#). The first 10 subjects who receive treatment dose for both capmatinib (BID) and spartalizumab for at least 12 weeks will be involved in the intensive PK cohort. If the 10 subjects are not recruited to the intensive PK cohort from the run-in part, the recruitment for the intensive PK cohort can extend into the randomized part of the study.

Table 8-11 Intensive PK cohort: Schedule of blood collection (plasma) for capmatinib (BID) PK

Cycle	Day	Scheduled Time (hours)	Dose Reference ID	Sample Number
3	1	Predose ^a	1/101 ^b	111
3	1	0.5 h (±5 minutes)	1	112
3	1	1 h (±10 minutes)	1	113
3	1	2 h (±15 minutes)	1	114
3	1	4 h (±30 minutes)	1	115
3	1	8 h (±2 hr)	1	116
4	1	Predose ^a	2/201 ^b	117
4	1	1 h (±10 minutes)	2	118
6	1	Predose ^a	3/301 ^b	119
6	1	1 h (±10 minutes)	3	120
8	1	Predose ^a	4	121
8	1	1 h (±10 minutes)	4/401 ^b	122
Unscheduled		Anytime		1001+

^a Take samples immediately prior to administration of capmatinib
^b The first Dose Reference ID (DRID) is for last dose the subject received prior to the collection of the PK sample, while the second DRID is for the current dose

Table 8-12 Sparse PK cohort: Schedule of blood collection (plasma) for capmatinib (BID) PK

Cycle	Day	Scheduled Time (hours)	Dose Reference ID	Sample Number
3	1	Predose ^a	1/101 ^b	211
3	1	1 h (±10 minutes)	1	212
4	1	Predose ^a	2/201 ^b	213
4	1	1 h (±10 minutes)	2	214
6	1	Predose ^a	3/301 ^b	215
6	1	1 h (±10 minutes)	3	216
8	1	Predose ^a	4	217
8	1	1 h (±10 minutes)	4/401 ^b	218
Unscheduled		Anytime		2001+

^a Take samples immediately prior to administration of capmatinib
^b The first Dose Reference ID (DRID) is for last dose the subject received prior to the collection of the PK sample, while the second DRID is for the current dose

8.5.2.3 Pharmacokinetic and immunogenicity (IG) sampling for Spartalizumab

Blood samples for spartalizumab and IG analysis will be collected as outlined in [Table 8-13](#) and [Table 8-14](#). The first 10 subjects who receive treatment dose for both capmatinib (BID) and spartalizumab for at least 12 weeks will be involved in intensive PK cohort. If the 10 subjects are not recruited to the intensive PK cohort from the run-in part, the recruitment for the intensive PK cohort can extend into the randomized part of the study.

If the dosing of Cycle 3 Day 1 is delayed, the PK sampling for the full PK profile should be delayed accordingly to match the scheduled time points for Cycle 3 as outlined in [Table 8-13](#). PK and IG samples will be collected also at the end of treatment visit and in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if IG is suspected. After the cut-off for the primary analysis is reached, no additional PK and IG samples will be collected for the subjects still ongoing in the study.

Table 8-13 Intensive PK cohort: schedule of blood collection (serum) for spartalizumab PK and IG

Cycle	Day	Scheduled Time (hours)**	Analytes	Dose Reference ID	PK Sample Number	IG Sample Number
1	1	Predose ^a	PK/IG [*]	11	41	51
1	15	336 h (± 24h)	PK	11	42	
2	1	Predose ^a	PK/IG [*]	11/12 ^c	43	52
3	1	Predose ^a	PK/IG [*]	12/13 ^c	44	53
3	1	1 h (± 5 min) ^b	PK	13	45	
3	4	72 h (± 8h)	PK	13	46	
3	8	168 h (± 8h)	PK	13	47	
3	15	336 h (± 24h)	PK	13	48	
4	1	Predose ^a	PK/IG [*]	13/14 ^c	49	54
6	1	Predose ^a	PK/IG [*]	15/16 ^c	50	55
8	1	Predose ^a	PK/IG [*]	17/18 ^c	51	56
10	1	Predose ^a	PK/IG [*]	19/20 ^c	52	57

Cycle	Day	Scheduled Time (hours) ^{**}	Analytes	Dose Reference ID	PK Sample Number	IG Sample Number
12	1	Predose ^a	PK/IG [*]	21/22 ^c	53	58
Every 6 cycles after C12D1 until discontinuation of study treatment	1	Predose ^a	PK/IG [*]	23/24 ^{c,d}	411+ ^e	511+ ^f
EOT		Anytime	PK/IG [*]		401	501
30-day safety follow-up		Predose ^a	PK/IG [*]		402	502
150-day safety follow-up ^g		Predose ^a	PK/IG [*]		403	404
Unscheduled		Anytime	PK/IG [*]		4001+	5001+

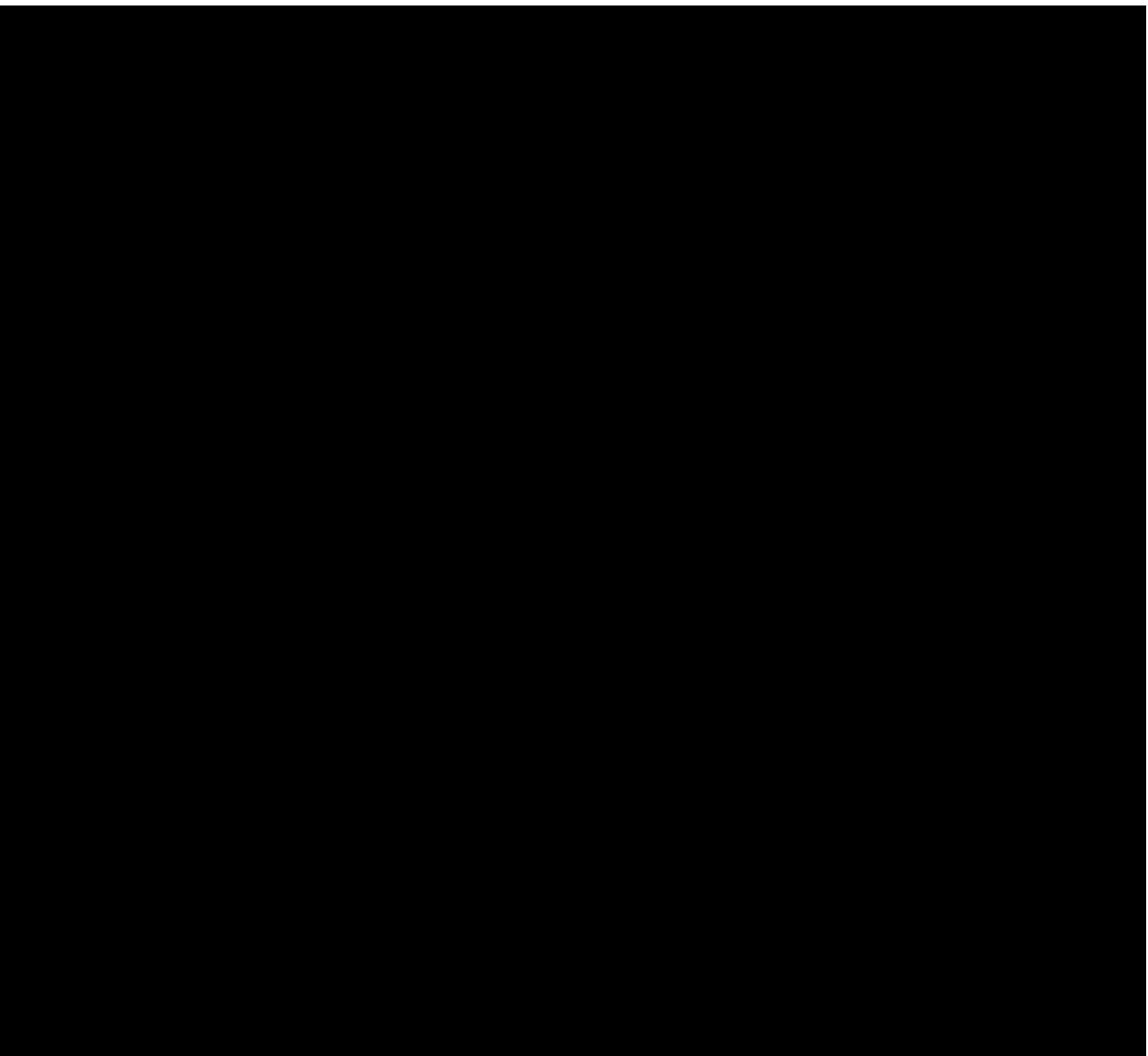
Table 8-14 Sparse PK cohort: schedule of blood collection (serum) for spartalizumab PK and IG

Cycle	Day	Scheduled Time (hours)**	Analytes	Dose Reference ID	PK Sample Number	IG Sample Number
1	1	Predose ^a	PK/IG [*]	11	61	71
1	15	336 h (± 24h)	PK	11	62	
2	1	Predose ^a	PK/IG [*]	11/12 ^b	63	72
3	1	Predose ^a	PK/IG [*]	12/13 ^b	64	73
3	15	336 h (± 24h)	PK	13	65	
4	1	Predose ^a	PK/IG [*]	13/14 ^b	66	74
6	1	Predose ^a	PK/IG [*]	15/16 ^b	67	75
8	1	Predose ^a	PK/IG [*]	17/18 ^b	68	76
10	1	Predose ^a	PK/IG [*]	19/20 ^b	69	77
12	1	Predose ^a	PK/IG [*]	21/22 ^b	70	78
Every 6 cycles after C12D1 until discontinuation of study treatment	1	Predose ^a	PK/IG [*]	23/24 ^{b,c}	611+ ^d	711+ ^e
EOT		Anytime	PK/IG [*]		601	701
30-day safety follow-up		Predose ^a	PK/IG [*]		602	702
150-day safety follow-up ^f		Predose ^a	PK/IG [*]		603	703
Unscheduled		Anytime	PK/IG [*]		6001+	7001+

Cycle	Day	Scheduled Time (hours)**	Analytes	Dose Reference ID	PK Sample Number	IG Sample Number
<p>^a Take samples immediately prior to the administration of spartalizumab.</p> <p>^b The first Dose Reference ID (DRID) is for last dose the subject received prior to the collection of the PK sample, while the second DRID is for the current dose.</p> <p>^c Dose reference ID will be labeled sequentially from 25, 26.....before EOT</p> <p>^d PK sample number will be labeled sequentially from 612, 613, 614,before EOT</p> <p>^e IG sample number will be labeled sequentially from 712, 713, 714,before EOT</p> <p>^f For patients who return to the site for 150-day onsite serum pregnancy test</p>						

8.5.2.4 Analytical methods

Pharmacokinetic samples for spartalizumab, capmatinib and its metabolite CMN288 will be quantified using validated LC/MS/MS assays. The assay to quantify and assess the IG will be a validated homogeneous ELISA.



9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Subjects may voluntarily discontinue from the study treatment for any reason at any time.

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration 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

- Subject/guardian decision
- Investigator decision
- Any situation in which study participation might result in a safety risk to the subject
- Adverse event requiring permanent discontinuation of study treatment as per [Section 6.5.3.1](#) and [Section 6.5.3.2](#)
- Progressive disease per RECIST 1.1 [REDACTED] (with the exception of continuation of treatment beyond disease progression.). Please see [Section 8.3](#) and [Section 6.1.5.1](#) for additional information.
- Protocol deviation that results in significant risk to subject's safety
- Use of prohibited treatment as per [Section 6.2.2](#)
- Pregnancy (Pregnancy may be followed for outcome as per [Section 10.1.4](#))
- Withdraw of consent (Please see [Section 9.1.2](#))
- Study is terminated by the sponsor (Please see [Section 9.1.4](#))

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

treatment and record this information. The investigator must also contact IRT to register the subject's discontinuation from study treatment.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent [Section 9.1.2](#)). **Where possible, they should return for the assessments indicated** in the assessment schedule (refer to [Table 8-2](#) and [Table 8-3](#)). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule (refer to [Table 8-2](#) and [Table 8-3](#)).

All subjects who discontinue study treatment should return for the safety assessments indicated in [Section 9.2.1](#), and if applicable, for the efficacy assessments indicated in [Section 9.2.2](#).

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 the assessment table.

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

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

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

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor, depending on the local regulations, will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

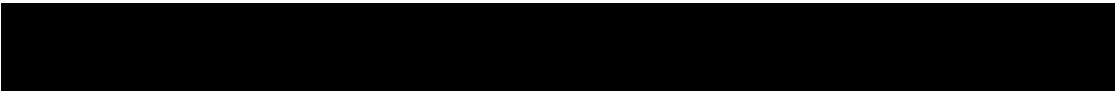
The primary analysis will be conducted when approximately 60 overall survival events are observed in the randomized phase of the study. The primary analysis data will be summarized in the primary clinical study report (CSR). Following the cut-off date for the analysis reported in the primary CSR, the study will remain open. As long as subjects derive benefit from study treatment, ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments, except for [REDACTED], PK assessments, and the Trial Feedback Questionnaire which will no longer be required.

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

- All subjects have died or discontinued from the study.
- Another clinical study becomes available that can continue to provide capmatinib and spartalizumab combination in this subject population, and all subjects ongoing are eligible to be transferred to that clinical study.

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting (e.g. Novartis managed access program) to subjects who, in the opinion of the investigator, are still deriving clinical benefit. The final analysis will occur at the end of the study. All available data from all subjects up to this cut-off date will be analyzed and summarized in a final CSR.

At the time of the end of this study, subjects continuing to derive benefit from docetaxel in the opinion of the investigator may continue such treatment at the Investigator's discretion according to local clinical practice, and every effort will be made to continue provision of study treatment outside this study through an alternative setting (e.g. Novartis managed access program) to subjects who, in the opinion of the investigator, are still deriving clinical benefit.



All treated subjects should have a safety follow-up visit conducted 30 days after last administration of study treatment. Due to the half-life of spartalizumab and the possible delayed onset of ADRs, subjects will be followed for safety up to 150 days after the last dose of spartalizumab. Please refer to [Section 9.2.1](#).

9.2.1 Follow up for safety evaluations

After treatment discontinuation, all subjects will be followed for safety evaluations and should have a safety follow-up after the last administration of the study treatment as per below:

Subjects treated with the capmatinib and spartalizumab combination

Due to the half-life of spartalizumab and the possible delayed onset of ADRs, subjects will be followed for safety up to 150 days after the last dose of spartalizumab or up to 30 days after the last dose of capmatinib, whichever was stopped last. All subjects will have a 30 day (+ 7 days) onsite safety follow-up visit, following which, subjects will be followed (via telephone call or onsite visit if subject happens to be visiting the site) at 60 (\pm 14 days), 90 (\pm 14 days), 120 (\pm 14 days) and 150 (+ 14) days after the last dose of spartalizumab. All safety assessments should be completed as per [Table 8-2](#). For female subjects of child-bearing potential, a pregnancy test will be performed at the time points listed in [Table 8-2](#). Please refer to the safety follow-up flow diagram in [Section 16.3](#).

If the subject begins any post-treatment antineoplastic medication before the 150 day safety follow-up period is complete, the collection of new SAEs and AEs unrelated to the capmatinib and spartalizumab combination will stop, and, thereafter, only suspected AEs and suspected SAEs will continue to be collected up to day 150. Suspected SAEs will continue to be collected beyond the 150 day safety visit.

Data collected should be added to the appropriate eCRF pages.

Subjects treated with docetaxel

Subjects randomized to the docetaxel arm will be contacted for an onsite safety follow-up 30 days after the last dose of docetaxel. For female subjects of child-bearing potential, a pregnancy test will be performed as listed in [Table 8-3](#). If the subject begins any post treatment antineoplastic medication before the 30 day safety follow-up period is complete, the collection of new SAEs and AEs unrelated to docetaxel will stop, and, thereafter, only suspected AEs and suspected SAEs will continue to be collected up to day 30. Suspected SAEs will continue to be collected beyond the 30 day safety visit.

Data collected should be added to the appropriate eCRF pages.

9.2.2 Follow up for efficacy evaluations

All subjects who discontinue study treatment for reasons other than initial disease progression as per RECIST 1.1, should continue tumor assessments at the same intervals as per [Table 8-2](#) and [Table 8-3](#) until treatment discontinuation criteria are met per [Section 9.1](#).

All subjects may be permitted to continue study treatment beyond initial disease progression as per RECIST 1.1. Please refer to [Section 6.1.5.1](#) for details.

9.2.3 Survival follow up

Subjects will enter the survival follow-up period once they complete the safety follow-up and efficacy follow-up after treatment discontinuation (whichever is longer). Subjects will then be contacted by telephone every 8 weeks to follow-up on their survival status. Any new antineoplastic therapies that have been started since the last contact date will also be collected during these phone calls.

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 the individual subject and identifying adverse events. Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events (including lab abnormalities that constitute AEs) must be recorded in the adverse events eCRF under the signs, symptoms or diagnosis associated with them, rather than individual underlying signs and symptoms and must be accompanied by the following information (as far as possible) (if the event is serious refer to [Section 10.1.2](#)):

- Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0
 - Grade 1 to 4 will be used to characterize the severity of the Adverse Event. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening (corresponding respectively to Grades 1 - 4) will be used.
- 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.
- Its duration (start and end dates) or if the event is ongoing. An outcome of not recovered/not resolved must be reported.
- Whether it constitutes a SAE (see [Section 10.1.2](#) for the definition of a SAE) and which seriousness criteria have been met.

- Action taken regarding with study treatment.

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

- Dose not changed
- Dose reduced/increased
- Drug interrupted/withdrawn
- Its outcome
 - Not recovered/not resolved;
 - Recovered/resolved;
 - Recovered/resolved with sequelae;
 - Fatal; or unknown.

If the event worsens, the event should be reported a second time in the 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 in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4. Conditions that were already present at the time of informed consent should be recorded in medical history eCRF of the subject.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and 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 the appropriate method (e.g., as per RECIST criteria for solid tumors), should not be reported as an adverse event, except if the investigator considers that progression of malignancy is related to study treatment. Adverse events separate from the progression of malignancy (for example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Abnormal laboratory values or test results constitute AEs 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.

Following the last dose of study treatment, AE monitoring should be continued as described in [Section 9.2.1](#).

Any AEs experienced after the follow-up safety evaluations timeframe as specified in [Section 9.2.1](#) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

Information about adverse drug reactions for the investigational drugs can be found in the [capmatinib Investigator's Brochure] and [spartalizumab Investigator's Brochure].

10.1.1.1 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, and include:

- For capmatinib:
 - Hepatotoxicity,
 - Pneumonitis/ILD,
 - Central nervous system toxicity,
 - Renal dysfunction,
 - Pancreatitis,
 - QTc interval prolongation,
 - Teratogenicity,
 - Phototoxicity,
 - Drug-drug interactions with strong CYP3A4 inducers
- For spartalizumab:
 - Endocrinopathies (i.e. hypothyroidism, hyperthyroidism, diabetes, hypophysitis and hypopituitarism, adrenal insufficiency),
 - Pneumonitis,
 - Colitis,
 - Hepatitis,
 - Nephritis,
 - Encephalitis,
 - Rash,
 - Other immune-mediated events,
 - Infusion reactions

Details regarding these adverse events are provided in the [capmatinib Investigator's Brochure] and the [spartalizumab Investigator's Brochure]. Potential emergent new AEs will be monitored during the course of the study.

10.1.2 Serious adverse events

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

- Fatal
- Life-threatening
 - Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines)
 - Results in persistent or significant disability/incapacity
 - Constitutes a congenital anomaly/birth defect
 - Requires subject 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 (e.g. loss of response, treatment failure)
 - 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 out-subject basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - Is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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 (progression of malignancy [including fatal outcomes], if documented by use of the appropriate method [e.g. for example, as per RECIST criteria for solid tumors], should not be reported as a serious adverse event.)

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 must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

The following SAE reporting time frames apply:

1. Screen Failures (e.g. a subject who is screened but is not treated or randomized): SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis
2. Randomized OR Treated Subjects: SAEs collected between the time the subject signs ICF until the timeframes specified in [Section 9.2.1](#) after the subject has discontinued or stopped study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A 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.

Any SAEs experienced after the follow-up safety evaluations timeframe as specified in [Section 9.2.1](#) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

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 males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration 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 the investigator's awareness.

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

Treatment error type	Document in Dose Administration (DAR) 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

For more information on AE and SAE definition and reporting requirements, please see [Section 10.1.1](#) and [Section 10.1.2](#).

10.2 Additional Safety Monitoring

Not applicable.

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 and allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into the 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 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 at specific timelines.

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. 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 Clinical Research Associate (CRA) 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 CRA during these visits.

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), in case of wet signature.

The investigator must give the CRA 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

The primary efficacy and safety analysis will be performed when approximately 60 overall survival events are observed in the randomized part. In the primary analysis, analysis of all primary, secondary, [REDACTED] objectives will be carried out.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all subjects in the run-in who received at least one dose of any component of study treatment and all subjects in the randomized part to whom study treatment has been assigned by randomization. In the randomized part according to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set includes all subjects who received at least one dose of study treatment (i.e. at least one dose of spartalizumab [including incomplete infusion or of capmatinib], or at least one dose of docetaxel [including incomplete infusion]). Subjects 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.

The Dose-Determining Set (DDS) includes all patients from the Safety Set in the run-in part who met the minimum exposure criterion and had sufficient safety evaluations, or experienced a dose limiting toxicity (DLT) during the first 56 days (8 weeks) of dosing.

A subject has met the minimum exposure criterion if the subject receives at least 1 infusion of spartalizumab and takes at least 50% of the planned dose of capmatinib within the first 8 weeks of treatment.

Subjects who do not experience a DLT during the first 56 days of dosing are considered to have sufficient safety evaluations if they have been observed for ≥ 56 days following the first dose, and are considered by both the sponsor and investigators to have enough safety data to conclude that a DLT did not occur.

The capmatinib pharmacokinetic analysis set (PAS-INC280) includes all subjects who provide at least one evaluable capmatinib PK concentration. For a concentration to be evaluable, subjects are required to:

- Take a planned 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 pharmacokinetic analysis set (PAS-PDR001) includes all subjects who provide at least one evaluable spartalizumab PK concentration. For a concentration to be evaluable, subjects are required to:

- Receive one of the planned treatments of spartalizumab prior to sampling.
- For pre-dose samples, have the sample collected before the next dose administration.
- For end-of-infusion samples, have the sample collected within 2 hours post end of infusion.

The immunogenicity (IG) set includes two parts: IG prevalence set and IG incidence set:

- The IG prevalence set includes all subjects in the Full analysis set with a determinant baseline IG sample or at least one determinant post-baseline IG sample.
- The IG incidence set includes all subjects in the IG prevalence set with a determinant baseline IG sample and at least one determinant post-baseline IG sample.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS and safety set.

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 separately by system organ class and preferred term, by treatment group.

12.3 Treatments

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

The duration of exposure in weeks to spartalizumab and capmatinib as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and 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 the study treatment by arm.

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

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

12.4 Analysis of the primary endpoint(s)

Primary Objectives

Part 1: Run-in

To assess safety and tolerability of capmatinib and spartalizumab combination in subjects with NSCLC, who have received one or more prior lines of systemic therapy for the locally advanced/metastatic stage of disease and are potential candidates for docetaxel single agent chemotherapy.

Part 2: Randomized

To assess the overall survival of combination of capmatinib and spartalizumab in comparison to docetaxel.

12.4.1 Definition of primary endpoint(s)

Part 1: Run-in

Incidence of DLTs during the first 8 weeks (56 days) of treatment for patients in the DDS.

Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, and ECGs.

Tolerability: Dose interruptions, reductions, and dose intensity.

Part 2: Randomized

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

12.4.2 Statistical model, hypothesis, and method of analysis

Part 1: Run-in

Assessing the safety and tolerability of capmatinib and spartalizumab combination will be based on the safety data including dose administration, adverse event, lab, vital signs and ECG data when all patients in this phase have at least 24 weeks of follow-up, pharmacokinetic data and preliminary efficacy data from all enrolled subjects in run-in phase. All dose administration data, safety, pharmacokinetic, and preliminary efficacy data will be listed for all subjects enrolled in the run-in.

The safety and tolerability assessment in run-in will be guided by a Bayesian analysis of DLT data for capmatinib and spartalizumab combination in the first 8 weeks (56 days) of treatment for subjects in the DDS. The relationship between dose and the probability of DLT is modeled using Bayesian logistic regression model (BLRM).

The dose-limiting toxicity (DLT) relationship is modeled by a 5-parameter BLRM that comprises single-agent toxicity parts and interaction part to describe the two-way drug safety interactions. Single agent toxicity is modeled using logistic regression for the probability of a subject experiencing a DLT against log-dose. The odds of a DLT for each dose regimen are then calculated under no interaction for the two single agent toxicities, and interaction is accounted for by adjusting these odds with additional model parameter (odds multiplier). Details of the model are provided in [Section 16.4](#).

After the run-in, posterior distributions for the risk of DLT will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

- Under-dosing: [0, 16%)
- Targeted toxicity: [16%, 33%)
- Excessive toxicity: [33%, 100%)

Assessing the safety and tolerability of the combination is guided by the EWOC principle ([Rogatko et al 2007](#)). A dose may be considered tolerable if the risk of excessive toxicity at that dose is < 25%.

Listing of DLTs

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

Part 2: Randomized

The primary analysis will be carried out when approximately 60 overall survival events are observed in the randomized phase of the study. The analysis of OS will be based on full analysis set which includes all randomized subjects. For the primary endpoint of OS, all the data collected up to the cut-off date for the analysis will be included. If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact. The estimated hazard ratio (HR) between capmatinib and spartalizumab combination and docetaxel and exact 80% confidence interval will be provided.

Capmatinib and spartalizumab combination is considered to have clinically relevant activity if the following two criterion are satisfied:

1. The observed HR of OS for capmatinib and spartalizumab combination vs docetaxel is ≤ 0.667 .
2. The upper limit of two sided 80% CI of HR of OS for capmatinib and spartalizumab combination vs docetaxel is < 1.0 .

Other efficacy data such as ORR, PFS, DCR, TTR, and DOR may be taken into consideration to assess clinically relevant activity.

12.4.3 Handling of missing values/censoring/discontinuations

Part 1: Run-in

Subjects who are excluded from the DDS will be excluded from the BLRM analysis of run-in part, although their data will be used for all the remaining analyses.

Part 2: Randomized

OS will be censored if no OS event is observed prior to the analysis cut-off date.

If a patient is not known to have died at the time of analysis cut-off, or lost to follow-up, OS will be censored at the date of last contact.

12.4.4 Sensitivity and supportive analyses

Sensitivity and supportive analyses may be conducted for the primary objective in the randomized part, if appropriate, and the details of these analyses will be defined in the SAP.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary efficacy endpoints, objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), time to response (TTR), duration of response (DOR) and disease control rate (DCR) based on the investigator assessed as per RECIST 1.1 as described in [Section 16.1](#) will be analyzed. Analysis of all secondary efficacy endpoints will be performed using the FAS.

- ORR is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR).
- Disease control rate (DCR) is defined as the proportion of subjects with best overall response of CR or PR or SD.
- Progression free survival (PFS) is defined as the time from the date of randomization (randomized part) or start of treatment (run-in part) to the date of the first documented radiological progression or death due to any cause.
- Time to response (TTR) is defined as the time from the date of randomization (randomized part) or start of treatment (run-in part) to the first documented response of either CR or PR, which must be subsequently confirmed (although date of initial response is used, not date of confirmation).
- Duration of response (DOR) only applies to subjects for whom best overall response is complete response (CR) or partial response (PR). DOR is defined as the time between the date of first documented response (CR or PR) and the date of first documented progression or death due to underlying cancer. If progression or death due to underlying cancer has not occurred, then the subject is censored at the date of last adequate tumor assessment.

ORR and DCR will be summarized with accompanying 95% confidence interval (CI). PFS, TTR, DOR and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented.

Individual lesion measurements and overall response assessments per RECIST 1.1 will be listed by assessment date. Best overall response per RECIST 1.1 will also be listed.

12.5.2 Safety endpoints

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment group.

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

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

1. Pre-treatment period: from the day of the subject's informed consent to the day before the first dose of study treatment.
2. On-treatment period: from the day of the first dose of study medication to 150 days after the last dose of spartalizumab, or 30 days after the last dose of capmatinib, whichever is later for the spartalizumab and capmatinib arm, or from the day of the first dose of study medication to 30 days after the last dose of docetaxel (including start and stop dates).
3. Post-treatment period: starting at 151 days after last dose of spartalizumab, or 31 days after last dose of capmatinib, whichever is later and 31 days after the last dose of docetaxel.

Adverse events

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period (the treatment-emergent AEs).

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, and relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest

(AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

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

Spartalizumab specific AESIs are defined in the case retrieval strategy (CRS) with regular updates whenever necessary, see also [Section 10.1.1.1](#). For each specified AESI, number and percentage of subjects with at least one adverse event (Preferred term) corresponding to the AESI will be reported.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time, and, if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12-lead ECG

- 12-lead ECGs including PR, QRS, QT, QTcF intervals and heart rate (HR) will be obtained for each subject during the study. ECG data will be read and interpreted locally.
- Categorical Analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced (by treatment group).

Clinical laboratory evaluations

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 applicable. For laboratory tests where grades are not defined by CTCAE v5.0, results will be categorized as low/normal/high based on laboratory normal ranges. The following listings/summaries will be generated separately for hematology, and biochemistry tests:

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

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

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

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

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

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 will be presented.

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

Immunogenicity

Immunogenicity will be characterized descriptively by tabulating anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment.

The impact of immunogenicity on PK, safety, and efficacy may be explored, and further details will be specified in the SAP.

12.5.3 Pharmacokinetics

The respective PAS for each study drug will be used in the pharmacokinetic data analysis.

Descriptive statistics (n, m number of non-zero concentrations, mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) for spartalizumab and capmatinib concentrations will be presented at each scheduled time point. All concentration data for spartalizumab and capmatinib will be displayed graphically.

Concentrations below LLOQ will be displayed in listings as zero with a flag and handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and their CV. Individual concentration-time profiles as well as mean concentration-time profile will be plotted when applicable.

PK parameters will be determined for intensive PK cohort in randomized part by applying non-compartmental method(s) using Phoenix WinNonlin version 6.4 or above (Pharsight, Mountain View, CA). The descriptive statistics (n, mean, CV%, standard deviation [SD], median, geometric mean, geometric CV%, minimum and maximum) will be presented for all PK parameters, including but not limited to those listed in [Table 12-1](#) except Tmax, where only n, median, minimum and maximum will be presented. Any missing PK parameter data will not be imputed.

Table 12-1 Non-compartmental pharmacokinetic parameters

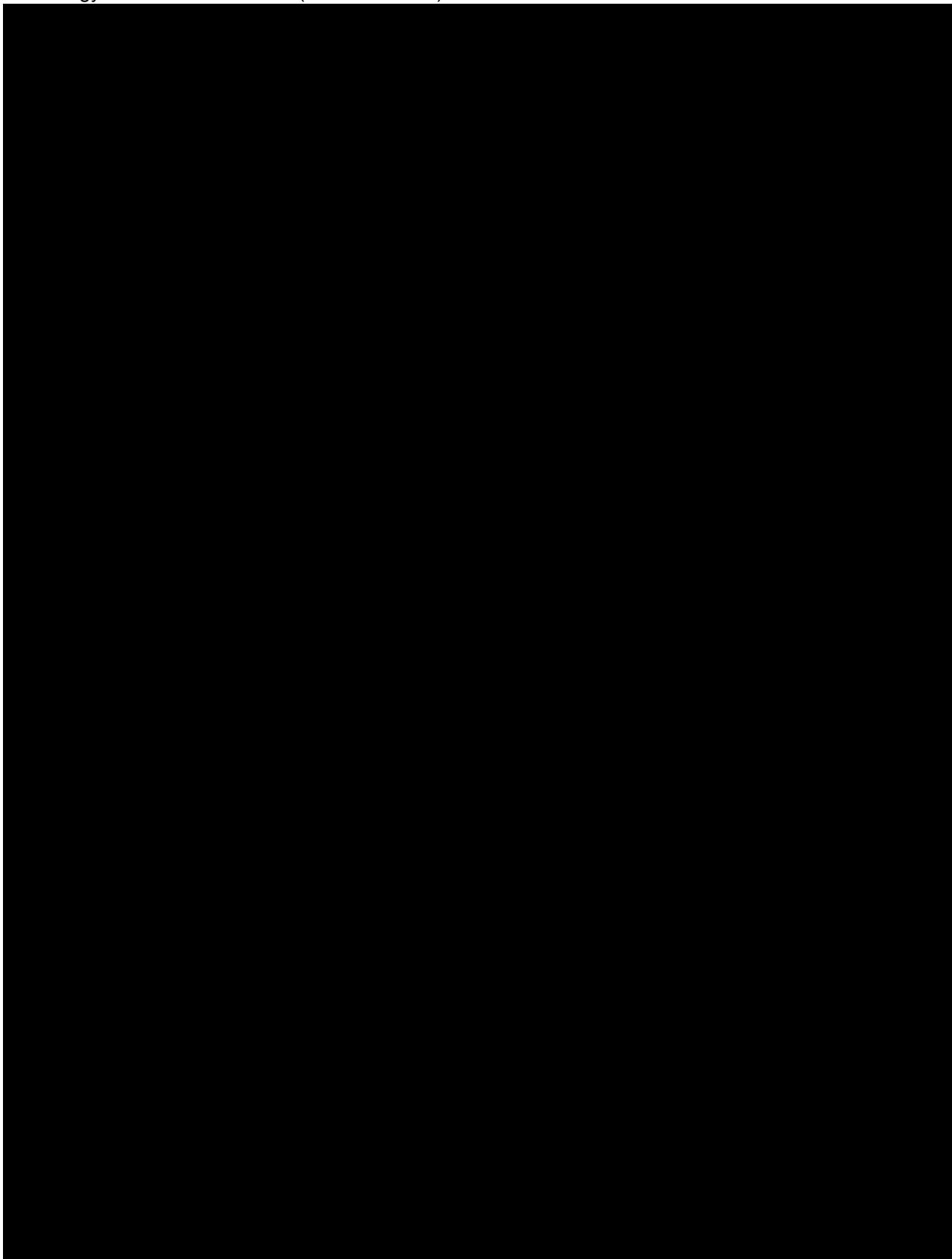
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma serum concentration after single dose administration (mass x volume-1)
Ctrough	The minimum (peak) observed plasma serum concentration (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)
T1/2	The elimination half-life associated with the terminal slope (l _z) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives

12.5.3.1 Handling of missing values/censoring/discontinuations

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

12.5.3.2 Population pharmacokinetic analysis

If data permit, a mixed-effects model may be applied to the spartalizumab and/or capmatinib concentration-time data to generate *post hoc* estimates of pharmacokinetic parameters using NONMEM 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.



12.7 Interim analyses

Not Applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

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

In the randomized part approximately 90 subjects will be randomized in a 2:1 ratio in this study; 60 subjects in capmatinib and spartalizumab combination arm and 30 subjects in docetaxel arm. The primary endpoint of the study will be overall survival. The sample size is based on observing a clinically relevant OS in capmatinib and spartalizumab combination arm compared to docetaxel arm.

The expected median OS for docetaxel as second-line chemotherapy is ~8 months ([Herbst et al 2016](#), [Rittmeyer et al 2017](#)). It is therefore reasonable to assume the median OS of ~8 months for docetaxel in this study and 33.3% reduction in hazard rate for overall survival in capmatinib plus spartalizumab arm compared to docetaxel arm, which corresponds to an increase in median OS by 4 months under the exponential assumption.

Therefore

- The HR of OS for capmatinib and spartalizumab combination vs docetaxel is ≤ 0.667
- The upper limit of two sided 80% CI of HR of OS for capmatinib and spartalizumab combination vs docetaxel is < 1.0

are considered clinically relevant activity in subjects in the capmatinib and spartalizumab combination arm.

Considering a 2:1 randomization, with approximately 60 OS events, the probability of observing clinically relevant activity is 66% when the true HR is 0.60 and the probability of observing clinically relevant activity is 24% when the true HR is 0.80. The operating characteristics are presented in [Table 12-2](#).

With 60 subjects in capmatinib and spartalizumab combination arm and 30 subjects in docetaxel arm, and assuming a median OS of 8 months in docetaxel arm and a HR of 0.66, 60 OS events will be observed in ~18 months with a recruitment rate of 15 subjects per month.

Table 12-2 Operating characteristics

True Median OS of docetaxel vs Median OS of capmatinib and spartalizumab	True HR	Probability of success (%)
6 vs 8	0.75	32.5
6 vs 10	0.60	65.9
6 vs 12	0.50	86.8
8 vs 8	1.0	5.8
8 vs 10	0.80	24.1
8 vs 12	0.66	50.0
8 vs 13	0.62	62.3
8 vs 14	0.57	72.5

12.8.2 Secondary endpoint(s)

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit, LPLV) and finalization of the study report, the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances, including incidental collection, is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

14.1 Protocol Amendments

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

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

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

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16 Appendices

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

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16.1.1 Introduction

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

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

16.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria ([Therasse et al 2000](#)), and revised RECIST guidelines (version 1.1) ([Eisenhauer et al 2009](#)).

16.1.2.1 Definitions

16.1.2.1.1 Disease measurability

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

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

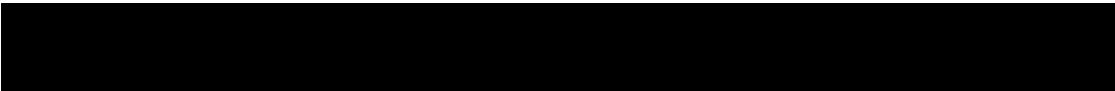
For patients without measurable disease see [Section 16.1.3.2.9](#).

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 \geq 15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring \geq 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 \geq 10 to <15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

16.1.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations. Guidance on how patients with just non-measurable disease at baseline will



be evaluated for response and also handled in the statistical analyses is given in [Section 16.1.3.2.8](#).

16.1.2.2 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm). 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.

If the protocol is considering specific symptoms as objective signs of clinical progression, e.g. bone pain or GI bleeding, then the criteria for clear worsening of these non-measurable ‘lesions’ indicative of PD should be clearly specified in the protocol. In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

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.

If tumor markers are used as non-target lesions to evaluate response, please specify criteria for CR, SD and PD in the protocol, e.g. CR='Normalization of tumor marker level', PD='Elevation of tumor markers to certain level', SD='Not qualifying for CR or PD'. These criteria are indication and study specific. In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

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 < 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 < 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.

Response Criteria	Evaluation of target lesions
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
	<p>1. SOD for CR may not be zero when nodal lesions are part of target lesions</p> <p>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</p> <p>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).</p>

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 < 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions < 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to < 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

Response Criteria	Evaluation of non-target lesions
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 .
<p>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.</p> <p>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)</p>	

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 16.1.3.2.8](#) outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.1.3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded

since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

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

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 7 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

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

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

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR ($\geq 30\%$ reduction of tumor burden compared to baseline) at one assessment, followed by a $<30\%$ reduction from baseline at the next assessment (but not $\geq 20\%$ 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
- Novartis calculated overall lesion response (based on measurements from Investigator)

The primary analysis of the best overall response will be based on the sequence of investigator//calculated (investigator) 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 time point for EPR is study specific. EPR is used for the multinomial designs of [Dent et al 2001](#) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks \pm 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.

16.1.3.2.4 PFS2

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

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

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

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

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

([FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics](#)) 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
C 1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment ²	Progressed Progressed
C 2	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/TPP/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/TPP/DoR analysis.

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

Additional suggestions for sensitivity analyses

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

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

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

16.1.4 Data handling and programming rules

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

16.1.4.1 Study/project specific decisions

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

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

16.1.4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-

up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

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

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

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

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

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

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

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

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

16.1.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available

evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

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

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

16.1.4.5 Programming rules

The following should be used for programming of efficacy results:

16.1.4.5.1 Calculation of 'time to event' variables

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

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

16.1.4.5.2 Incomplete assessment dates

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

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

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

16.1.4.5.3 Incomplete dates for last known date patient alive or death

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

16.1.4.5.4 Non-target lesion response

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

16.1.4.5.5 Study/project specific programming

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

16.1.4.5.6 Censoring reason

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

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

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

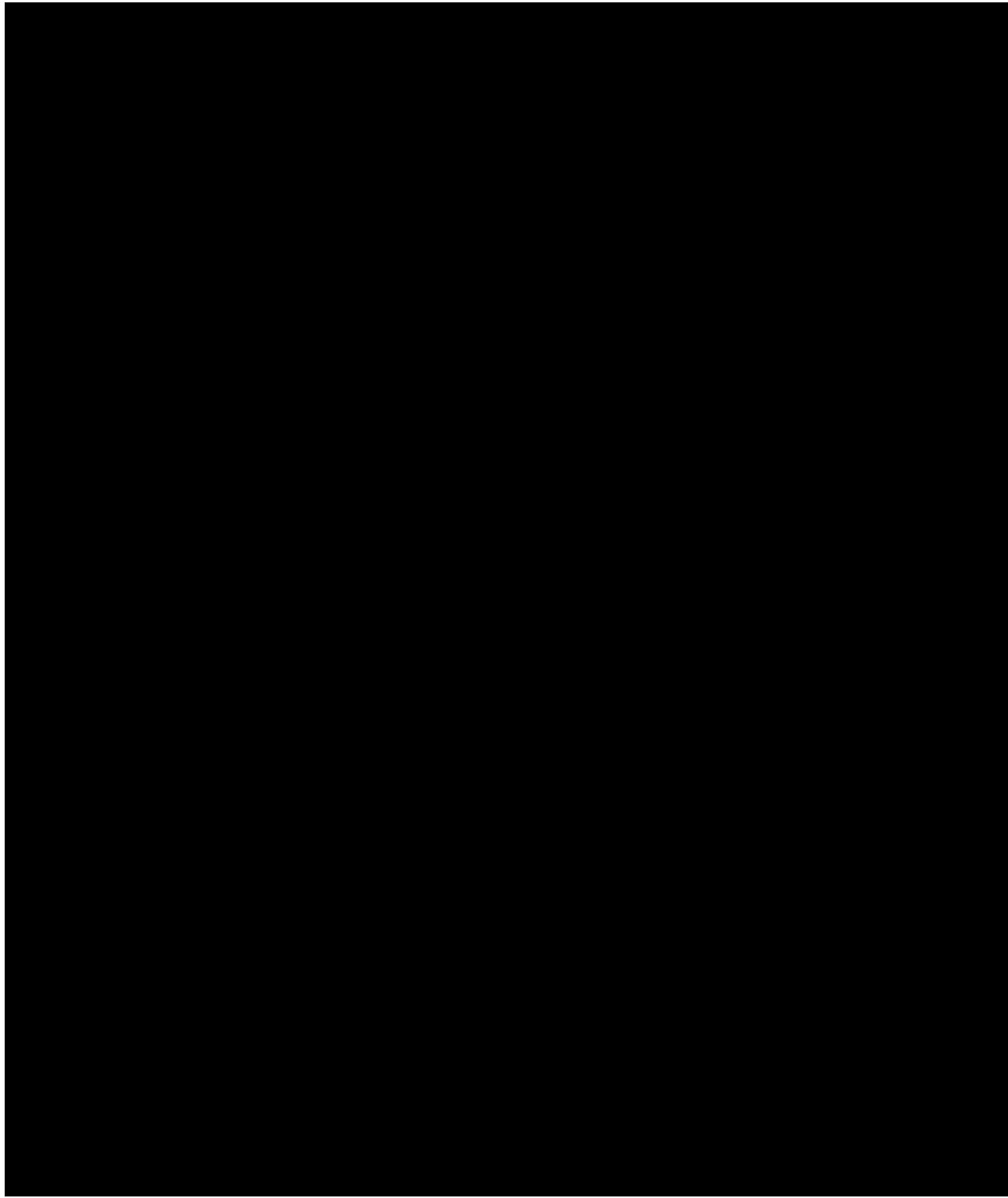
- Ongoing without event
- Lost to follow-up
- Withdraw consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see [Table 16-5](#))
- Death due to reason other than underlying cancer (*only used for TTP and duration of response*)
-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

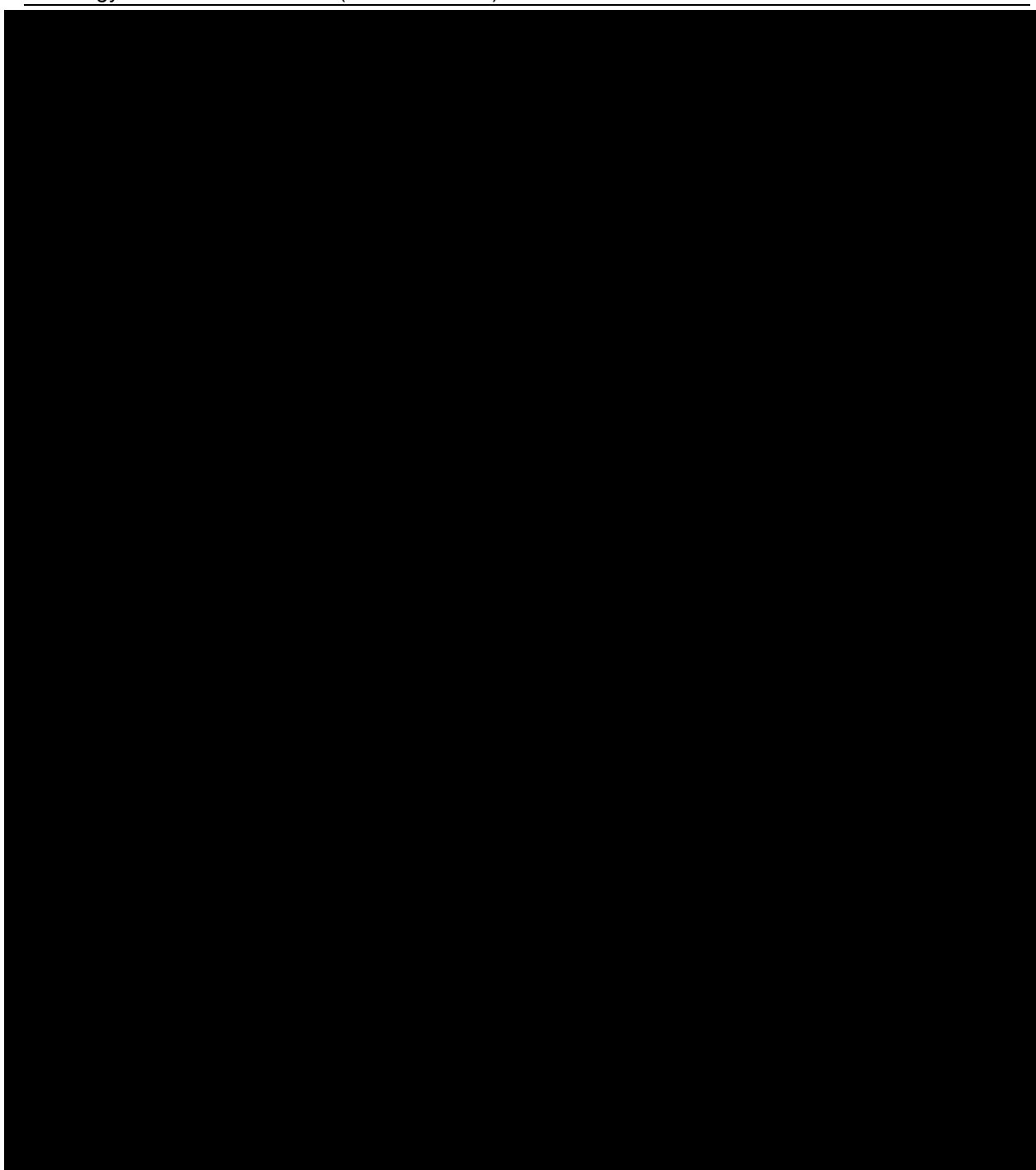
* Adequate assessment is defined in [Section 16.1.3.2.7](#). This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the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

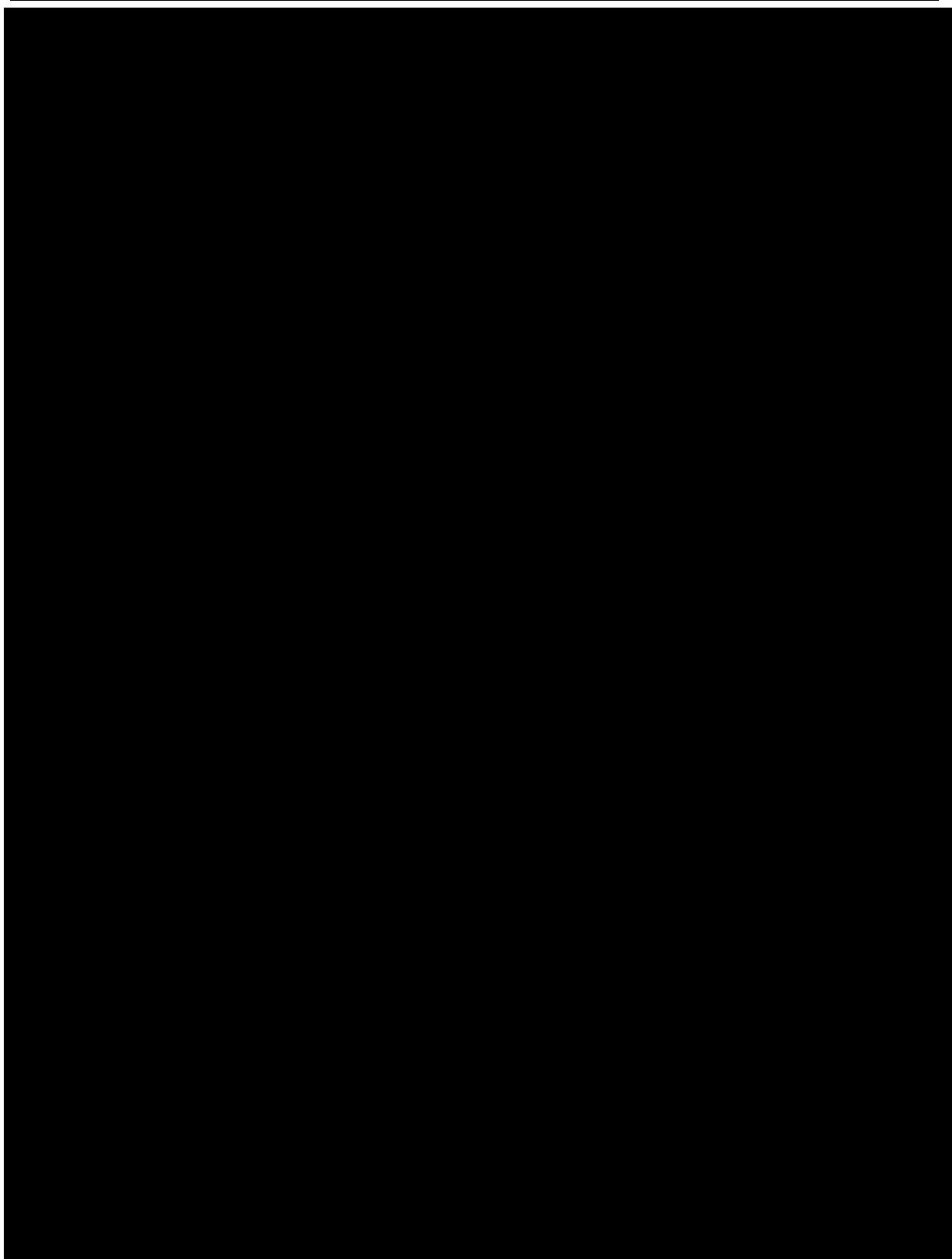
- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off.
- The reason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

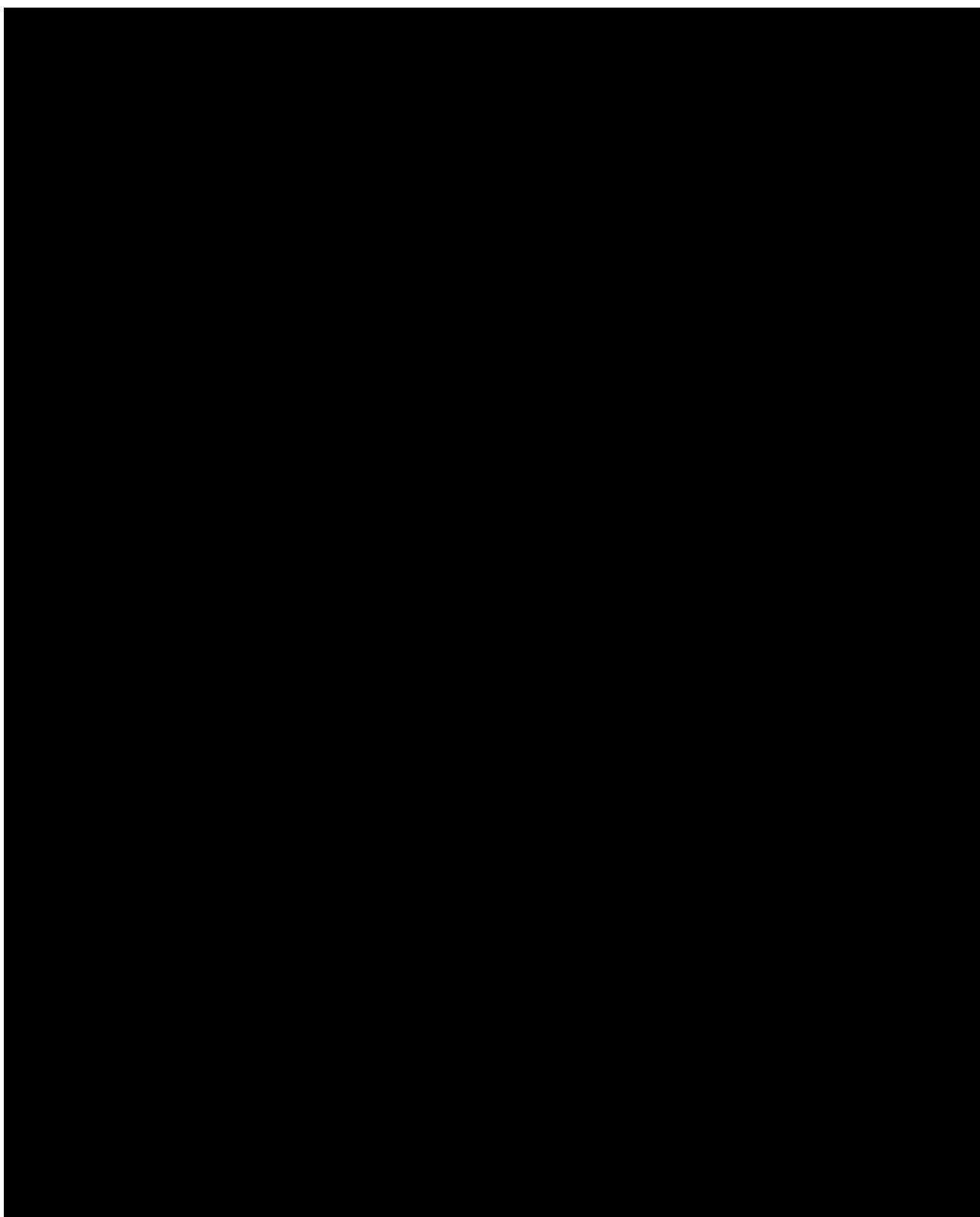
cancer therapy) has occurred more than the specified period following the last adequate assessment.

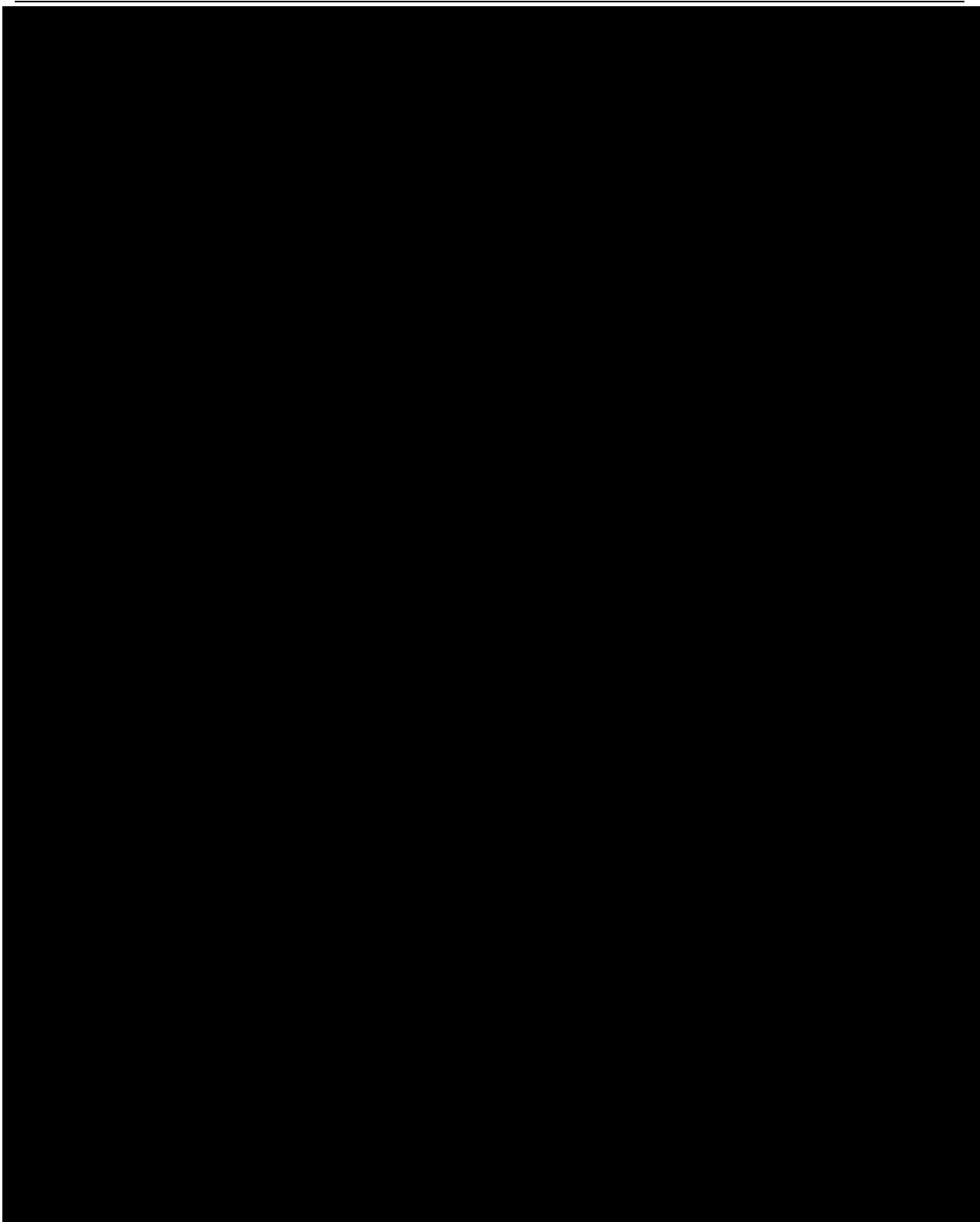
- This reason will also be used to censor in case of no baseline assessment.

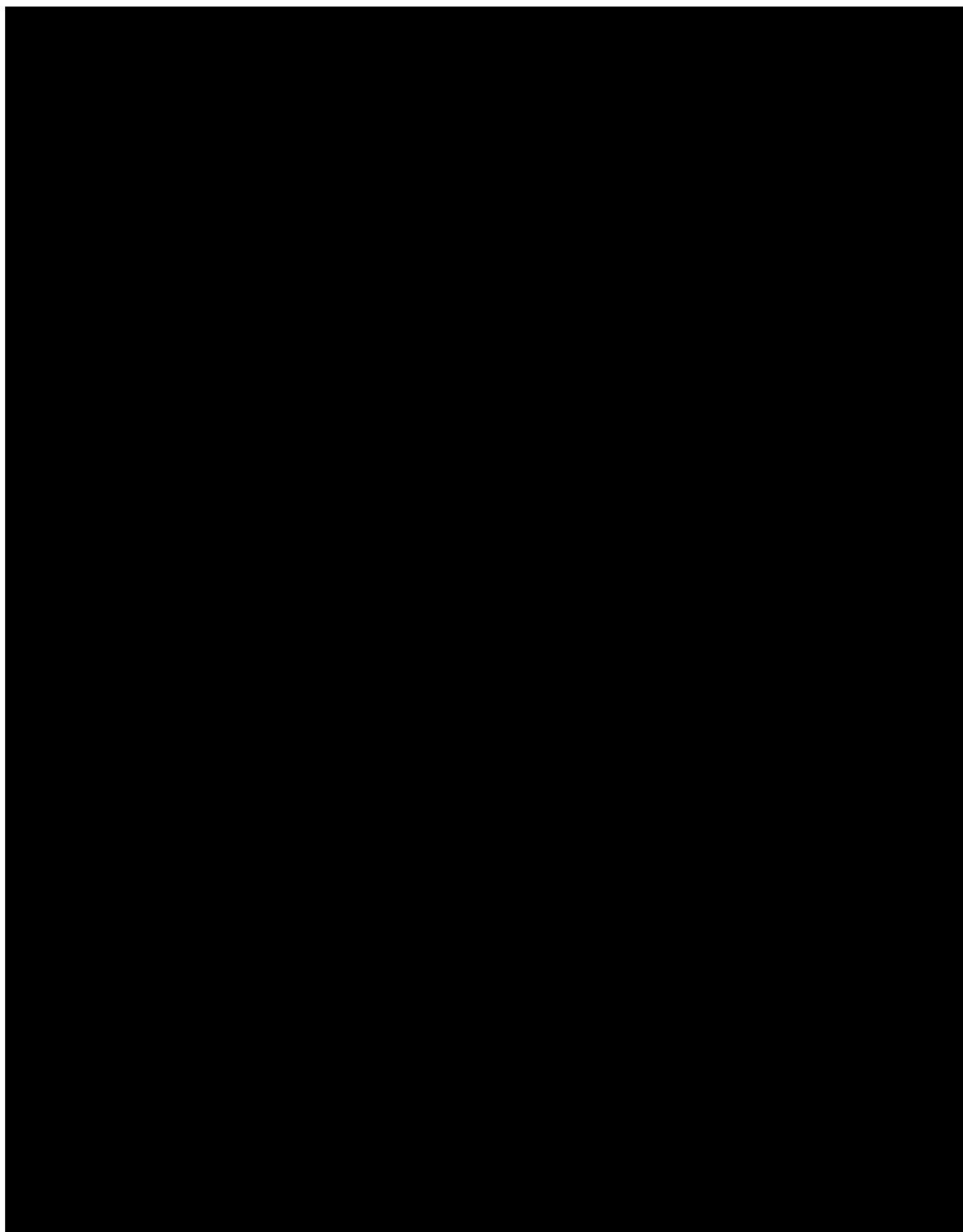


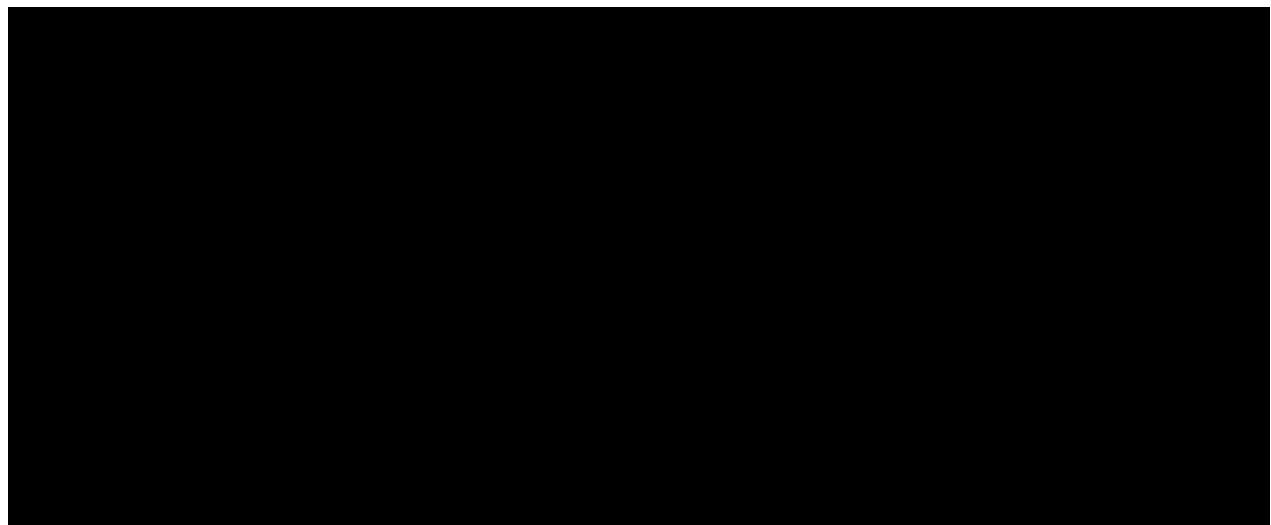
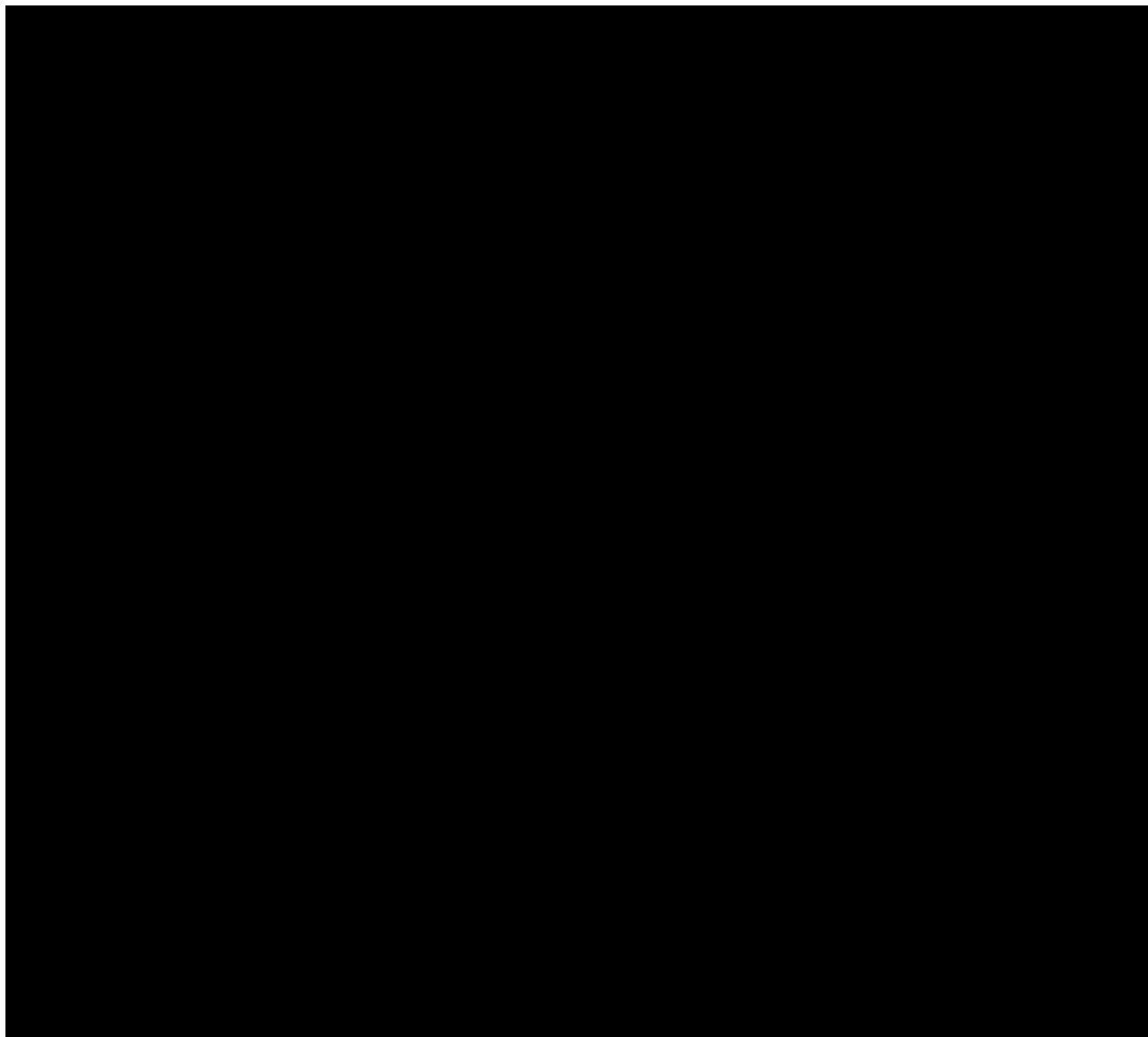


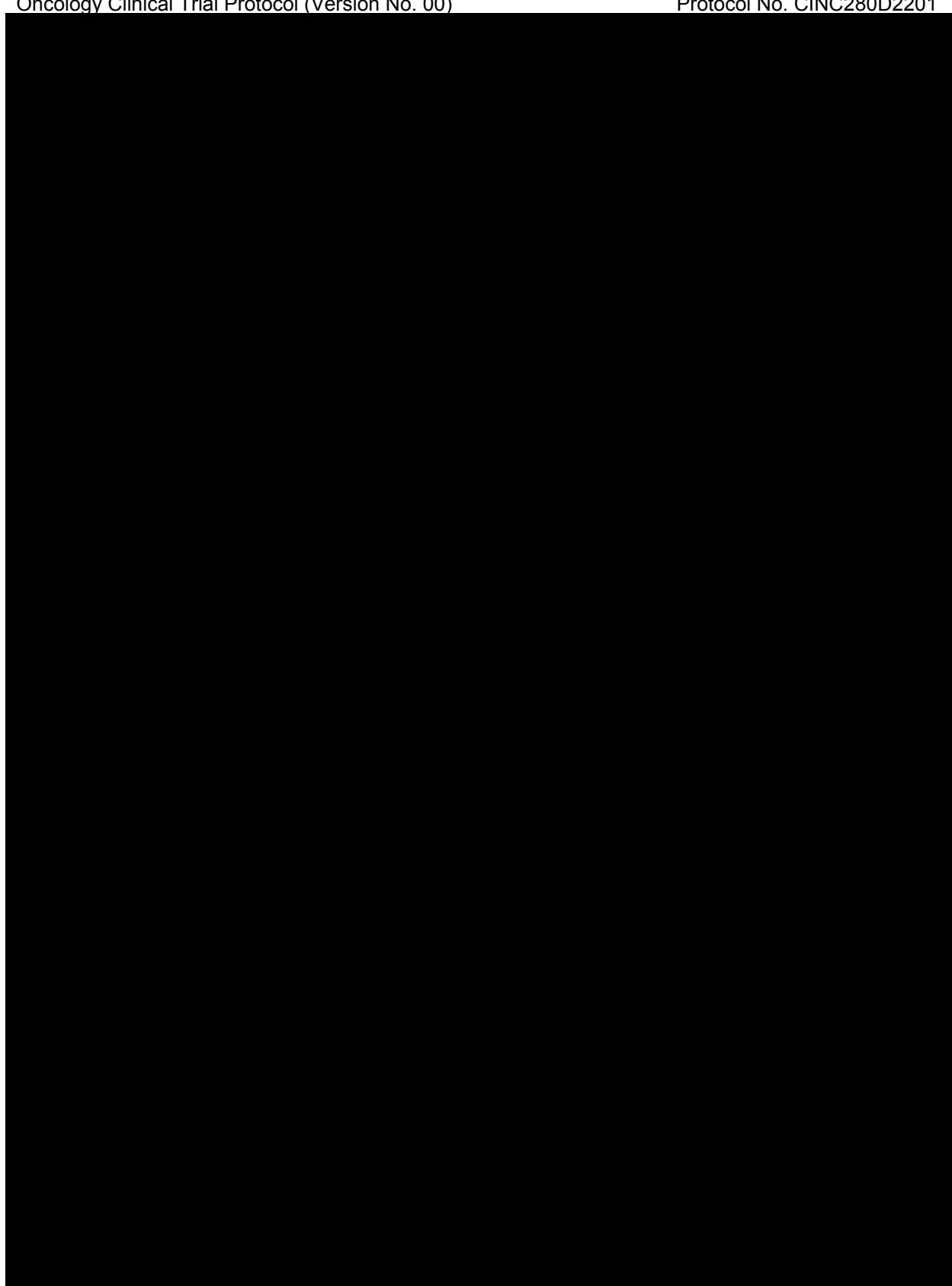


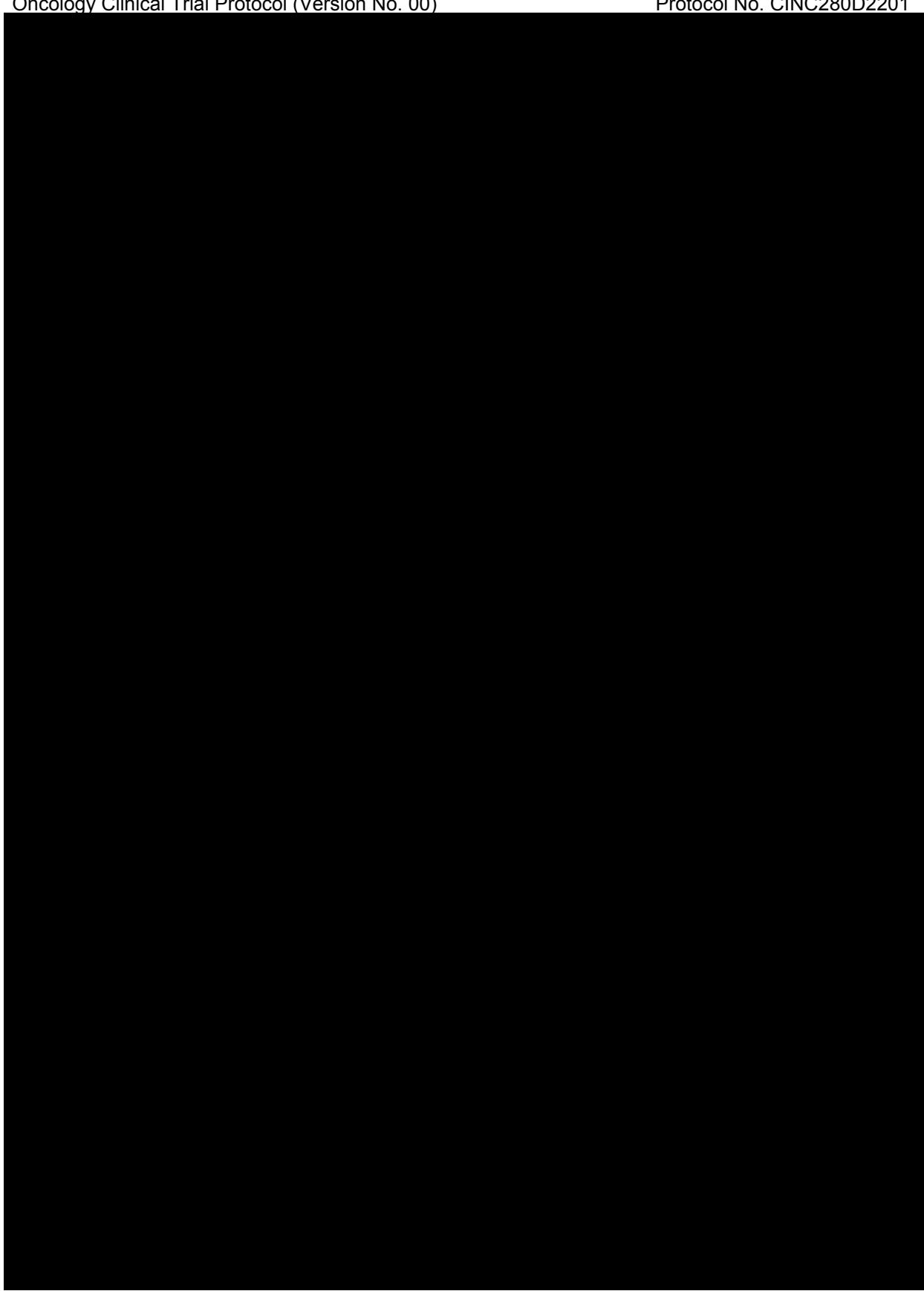






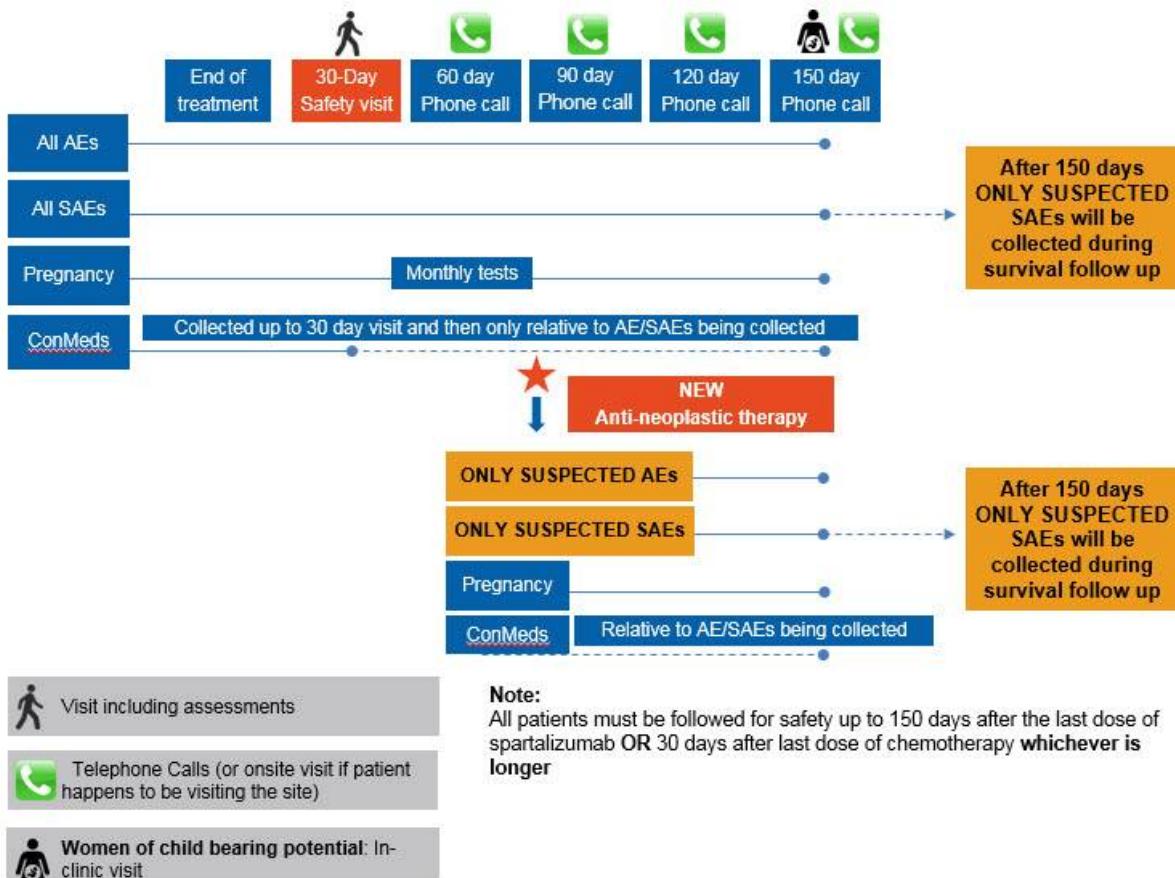






16.3 Appendix 3: Safety follow-up diagram

Figure 16-1 Safety follow-up diagram for run-in and arm 1



conMeds: concomitant medications

16.4 Appendix 4: Bayesian logistic regression model (BLRM)

This appendix provides details of the statistical model, the derivation of prior distributions from historical data, and the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios.

16.4.1 Statistical model

The statistical model comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and an interaction part.

16.4.1.1 Single agent parts

Let $\pi^{INC}(d^{INC})$ be the risk of DLT for capmatinib given as a single agent at dose d^{INC} ; $\pi^{PDR}(d^{PDR})$ be the risk of DLT for spartalizumab given as a single agent at dose d^{PDR} . Single agent toxicity is modelled using logistic regression for the risk of DLT against log-dose:

Capmatinib: $logit(\pi^{INC}(d^{INC})) = \log(\alpha^{INC}) + \beta^{INC} \log(d^{INC}/400)$

Spartalizumab: $logit(\pi^{PDR}(d^{PDR})) = \log(\alpha^{PDR}) + \beta^{PDR} \log(d^{PDR}/400)$

where 400mg is used to scale the doses of both capmatinib and spartalizumab. Hence, α^{INC} and $\alpha^{PDR} (>0)$ are the single-agent odds of a DLT at 400mg (BID, total daily dose 800mg) and 400mg (q4w), respectively; and β^{INC} and $\beta^{PDR} (>0)$ are the increase in the log-odds of a DLT by a unit increase in log-dose for capmatinib and spartalizumab respectively.

The statistical model comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and an interaction part.

16.4.1.2 Interaction

Under no interaction, the risk of a DLT at dose d^{INC} of capmatinib and dose d^{PDR} of spartalizumab is:

$$\pi_0^{comb}(d^{INC}, d^{PDR}) = 1 - (1 - \pi^{INC}(d^{INC})) (1 - \pi^{PDR}(d^{PDR}))$$

To allow for interaction between capmatinib and spartalizumab, an odds multiplier is introduced. The risk of DLT for combination dose (d^{INC}, d^{PDR}) is then given by:

$$odds(\pi^{comb}(d^{INC}, d^{PDR})) = \exp(\eta \times d^{INC}/400 \times d^{PDR}/400) \times odds(\pi_0^{comb}(d^{INC}, d^{PDR})),$$

where $odds(\pi) = \pi / (1 - \pi)$; and η is the log-odds ratio between the interaction and no interaction model at the reference doses. Here $\eta = 0$ corresponds to no interaction, with $\eta > 0$ and $\eta < 0$ representing synergistic and antagonistic toxicity respectively.

16.4.2 Prior specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\alpha^{INC})$, $\log(\beta^{INC})$ for capmatinib, $\log(\alpha^{PDR})$, $\log(\beta^{PDR})$ for spartalizumab, and the interaction parameter η . A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters based upon available DLT data.

16.4.2.1 Prior distribution for the logistic parameters

Description of the meta-analytic-predictive (MAP) approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters ($\log(\alpha^*), \log(\beta^*)$) of the new trial using DLT data from historical studies.

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical trial s ($s = 1, \dots, S$). The corresponding probability of a DLT is π_{ds} . The model specifications for the derivation of the MAP prior are as follows:

$$\begin{aligned} r_{ds} \mid \pi_{ds} &\sim \text{Bin}(\pi_{ds}, n_{ds}) \\ \text{logit}(\pi_{ds}) &= \log(\alpha_s) + \beta_s \log(d / d_{ref}) \\ (\log(\alpha_s), \log(\beta_s)) \mid \mu, \Psi &\sim \text{BVN}(\mu, \Psi), s = 1, \dots, S \\ (\log(\alpha^*), \log(\beta^*)) \mid \mu, \Psi &\sim \text{BVN}(\mu, \Psi) \end{aligned}$$

where d_{ref} is the reference dose. The parameters $\mu = (\mu_1, \mu_2)$ and Ψ are the mean and between-trial covariance matrix for the logistic parameters, the latter with standard deviations τ_1, τ_2 , and correlation ρ . The parameters τ_1 and τ_2 quantify the degree of between trial heterogeneity. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2 ,
- log-normal priors for τ_1 and τ_2 , and
- a uniform prior for ρ .

The MAP prior for single-agent model parameters in the new trial, $(\log(\alpha^*), \log(\beta^*))$, is the predictive distribution

$$(\log(\alpha^*), \log(\beta^*)) \mid (r_{ds}, n_{ds} : s = 1, \dots, S)$$

Since the predictive distribution is not available analytically, MCMC is used to simulate values from this distribution. This is implemented using JAGS version 3.4.0. The sample from this distribution is then approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster et al 1977, Wu CFJ 1983). The optimal number of components of the mixture is then identified using the Akaike information criterion (Akaike 1974).

Single agent capmatinib

For the MAP model for capmatinib, reference dose $d_{ref} = 400$ mg (BID) is used, and data from $S = 2$ historical studies are available.

Weakly informative normal priors are assumed for μ_1 and μ_2 , with means corresponding to an assumed 10% risk of DLT at the reference dose of 400 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander et al 2010).

The prior distributions for the model used for deriving the MAP priors are specified in Table 16-9.

Table 16-9 Prior distributions for the parameters of the MAP model used to derive the prior for the single-agent capmatinib model parameters

Parameter	Prior distribution
μ_1	$N(\text{mean} = \text{logit}(0.1), \text{sd} = 2)$
μ_2	$N(\text{mean} = 0, \text{sd} = 0.001)$
τ_1	$\text{log-normal}(\text{mean} = 0.25, \text{sd} = \text{log}(2)/1.96)$
τ_2	$\text{log-normal}(\text{mean} = 0.125, \text{sd} = \text{log}(2)/1.96)$
ρ	$\text{uniform}(-1, 1)$

Historical data

The dose-DLT data of capmatinib single agent in tablet formulation and BID dosing schedule from the following clinical studies are considered as the relevant information (Table 16-10) and used to derive the prior distribution for the BLRM parameters ($\log(\alpha^{INC})$, $\log(\beta^{INC})$).

- **CINC280X2102:** a Phase I study on adult patients with MET dependent advanced solid tumors.
- **CINC280X1101:** a Phase I study of capmatinib in Japanese adult patients with advanced solid tumors.

The DLT observation window was 4 weeks in both trials. The AE records of the patients did not show any events that had occurred during the 5th and 6th weeks post-baseline and met the specified DLT criteria.

Table 16-10 Historical dose-DLT data from capmatinib single agent clinical studies

Dose in BID (mg)	Number of evaluable patients	Number of DLTs
CINC280X2102		
400	4	0
CINC280X1101		
200	3	0
400	10	1

Single agent spartalizumab

The prior distribution of spartalizumab single agent BLRM model parameters ($\log(\alpha^{PDR})$, $\log(\beta^{PDR})$) is a mixture of two components: a MAP prior, and a robustification component, used to allow for a dose/toxicity relationship for spartalizumab in combination that differs substantially from that in single agent. The components form a mixture prior with respective weights (0.95, 0.05).

Component 1:

For the MAP model for spartalizumab, reference dose d_{ref} = mg (q4w) is used, and data from $S = 1$ historical studies is available.

Weakly informative normal priors are assumed for μ_1 and μ_2 , with means corresponding to an assumed 10% risk of DLT at the reference dose of 400 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander et al 2010).

The prior distributions for the model used for deriving the MAP priors are specified in [Table 16-11](#).

Table 16-11 Prior distributions for the parameters of the MAP model used to derive the prior for the single-agent spartalizumab model parameters

Parameter	Prior distribution
μ_1	$N(\text{mean} = \text{logit}(0.1), \text{sd} = 2)$
μ_2	$N(\text{mean} = 0, \text{sd} = 0.001)$
τ_1	$\text{log-normal}(\text{mean} = 0.25, \text{sd} = \text{log}(2)/1.96)$
τ_2	$\text{log-normal}(\text{mean} = 0.125, \text{sd} = \text{log}(2)/1.96)$
ρ	$\text{uniform}(-1, 1)$

Historical data

The dose-DLT data of spartalizumab single agent from the following clinical study are considered as the relevant information ([Table 16-12](#)) and used to derive the prior distribution for the BLRM parameters ($\log(\alpha^{PDR})$, $\log(\beta^{PDR})$).

- **CPDR001X2101:** open label multicenter Phase I/II study of the safety and efficacy of spartalizumab administered to patients with advanced malignancies.

The DLT observation window in the Phase I dose escalation part of this trial was 4 weeks. The 6-week AE records of the patients did not show difference from the 4-week data in DLT observation. It is assumed that DLT rate is associated with total exposure of PDR001 within the observation window, and the average weight of a patient is 80 kg. Then each dose level in the historical data $d_{qKw}[\text{mg/kg}]$ ($K = 2$ or 4) can be converted to a flat dose level in a q4w dosing schedule, $d_{q4w} [\text{mg}]$, using the following:

$$d_{q4w} [\text{mg}] = d_{qKw}[\text{mg/kg}] * 80[\text{kg}] / K[\text{week}] * 4[\text{week}].$$

Table 16-12 Historical dose-DLT data from spartalizumab single agent clinical studies

Dosing schedule	Dose level (mg/kg)	Converted to dose level in q4w (mg)	Number of evaluable patients	Number of DLTs
q2w	1	160	16	0
q2w	3	480	15	0
q2w	10	1600	8	0
q4w	3	240	6	0
q4w	5	400	10	0

Component 2:

To take into account the potential situation that spartalizumab in combination is substantially more toxic than when administered as single agent, and that the longer DLT period of 56 days may increase the chance of experiencing toxicity, a second high-toxicity prior component with vague bivariate normal distribution is added to improve the robustness of the final prior. The parameters of this weekly informative prior distribution are described below:

- The mean ($\log(\alpha_{(c2)}^{PDR})$, $\log(\beta_{(c2)}^{PDR})$) = ($\text{logit}(0.33)$, 0), i.e. the median DLT rate at the reference dose (400 mg) was assumed to be 0.33 and doubling in dose was assumed to double odds of DLT.

- The standard deviations of $\log(\alpha_{(c2)}^{PDR})$ and $\log(\beta_{(c2)}^{PDR})$ are set to 2 and 1, respectively.
- The correlation between $\log(\alpha_{(c2)}^{PDR})$ and $\log(\beta_{(c2)}^{PDR})$ is set to 0, assuming independence.

16.4.2.2 Prior distribution for the interaction parameter

Although no interaction is expected for the two agents, uncertainty remains. Therefore, a normal prior for the log-odds multiplier η centered at 0 is used that allows for both synergistic and antagonistic toxicity. The following assumptions will be used for interaction parameter.

- η is normally distributed, with mean 0, and standard deviation
- At the run-in dose of 400mg (BID) capmatinib in combination with 400mg spartalizumab q4w, η distribution corresponds to a best guess of no interaction and a 97.5% probability of having more than 2-fold increase in odds of DLT due to interaction compared to no interaction for capmatinib in combination with spartalizumab

Additional historical data for capmatinib and spartalizumab combination

The dose-DLT data for the combination from CINC280X2108 are considered as relevant information ([Table 16-13](#)) and will be incorporated into the prior model using discounted weighting.

CINC280X2108: A phase Ib/II, open-label, multi-center study of capmatinib in combination with spartalizumab or spartalizumab single agent in advanced hepatocellular carcinoma

The DLT observation window was 6 weeks.

Data from CINC280X2108 will be incorporated into the prior model using discounted weighting, where weight is determined as:

$\text{weight} = 1 / (1 + 2n\tau^2 / sd^2)$, where n refers to study sample size and τ and sd correspond to the assumed mean and standard deviation for between-trial heterogeneity. In this case, a moderate between-trial heterogeneity is assumed ($\tau = 0.250$, $sd = 2$).

Table 16-13 Historical dose-DLT data from capmatinib in combination with spartalizumab 300 mg Q3W

Capmatinib dose in BID (mg)	Number of evaluable patients	Number of DLTs	Weight to be used in prior model
CINC280X2108			0.62
200	5	0	
300	6	0	
400	9	1	

16.4.2.3 Summary of prior distributions

The prior distributions of the model parameters are summarized in [Table 16-14](#). The prior distribution of DLT rates are summarized in [Table 16-15](#).

Table 16-14 Prior distribution for the model parameters

Parameter	mean	Standard deviations	correlation	weight
Capmatinib single agent model				

Parameter	mean	Standard deviations	correlation	weight
$(\log(\alpha^{NC}), \log(\beta^{NC})) \sim \text{BVN}$				
(MAP)	(-2.848, 0)	(1.012, 0)	0	1
Spartalizumab single agent model				
$(\log(\alpha^{PDR}), \log(\beta^{PDR})) \sim \text{BVN mixture}$				
Component 1	(-5.034, 0)	(1.199, 0.141)	0.003	0.95
(MAP)				
Component 2	(-0.708, 0)	(2, 1)	0	0.05
(robustification)				
Interaction parameter				
Normal				
η	0	0.354	N/A	N/A

Table 16-15 Summary of prior distribution of DLT rates

Capmatinib BID dose (mg)	Prior probabilities that P(DLT) is in the interval :			Quantiles				
	[0, 0.16)	[0.16, 0.33)	[0.33,1]	Mean	SD	2.5%	50%	97.5%
In combination with spartalizumab 400 mg Q4W								
capmatinib =400	0.915	0.081	0.004	0.078	0.057	0.013	0.064	0.227

16.4.2.4 Hypothetical data scenarios

To illustrate the performance of the Bayesian model used to guide the run-in part, hypothetical DLT scenarios are displayed. In each case, the possibility of going to the randomized phase is shown. The safety and tolerability of the dose is determined using the model based assessment of the risk of DLT in future patients and the rules as described in [Section 6.5.1](#).

The dose may be recommended to continue if probability of excessive toxicity (i.e. DLT rate $\geq 33\% < 0.25$), satisfying the EWOC criteria.

Table 16-16 Hypothetical DLT scenarios

Scenario	Number of Patients	Number of DLTs	Posterior probabilities	
			Median P(DLT)	P(excessive toxicity)
1	10	5	0.224	0.159
2	10	6	0.227	0.318
3	12	6	0.251	0.222
4	12	7	0.298	0.388
5	15	7	0.259	0.233
6	15	8	0.304	0.395

If ≤ 5 DLT's are observed in 10 evaluable patients in run-in, the probability of excessive toxicity satisfies the EWOC criteria.

If ≥ 6 DLT's are observed in 10 evaluable patients in run-in, the probability of excessive toxicity do not satisfy the EWOC criteria. In this case, it would be recommended to stop the study.

If ≤ 6 DLT's are observed in 12 evaluable patients in run-in, the probability of excessive toxicity satisfies the EWOC criteria.

If ≥ 7 DLT's are observed in 12 evaluable patients in run-in, the probability of excessive toxicity do not satisfy the EWOC criteria. In this case, it would be recommended to stop the study.

If ≤ 7 DLT's are observed in 15 evaluable patients in run-in, the probability of excessive toxicity satisfies the EWOC criteria.

If ≥ 8 DLT's are observed in 15 evaluable patients in run-in, the probability of excessive toxicity do not satisfy the EWOC criteria. In this case, it would be recommended to stop the study.