NOVARTIS

Clinical Development

INC280/Capmatinib

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

Statistical Analysis Plan (SAP)

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Document type: SAP Amendment 1

Document status: Final

Release date: 05-Oct-2020

Number of pages: 45

Document History – Changes compared to previous final version of SAP

Date	Version	Reason for update	Outcome for update
04-Oct-2018	*1.0*	*N/A*	*N/A - First version*
05-Oct-2020	*2.0 (Amemdment 1)*	*Decision not to start randomization part*	*Only a final CSR will be prepared as an abbreviated report based on the data from run-in part and with reduced analyses.*

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
Bid	bis in diem/twice a day
CD8	Cluster of differentiation 8
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DDS	Dose Determining Set
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IHC	Immunohistochemistry
irRECIST	Immune-related RECIST
IVR	Interactive Voice Response
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NSCLC	Non-small Cell Lung Cancer
o.d.	Once Daily
OS	Overall Survival
PD-1	Programmed Death 1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
[redacted]	[redacted]
qd	Qua'que di'e / once a day
[redacted]	[redacted]
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This abbreviated statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Reports (CSRs) of study CINC280D2201, 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.

The content of this SAP is based on protocol [CINC280D2201-v00--protocol]. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

During the run-in part of the study (18 subjects enrolled), we explored the safety and preliminary efficacy of this combination testing the hypothesis of immunomodulatory and synergistic activity of capmatinib with spartalizumab in subjects previously treated with platinum and checkpoint inhibitor (anti-PD(L)-1).

The primary objective for the run-in part (safety) was met with no new safety signal observed. Nevertheless the preliminary efficacy data, suggests early on that the probability to observe the strong efficacy signal in proof of concept randomized part, which will lead to change of standard of care, is low. Based on these preliminary results, the randomized part of the study will not be opened.

In consideration of the early permanent recruitment halt and given that the randomized part of the study will not be opened, the final analysis will not be performed as originally planned for all endpoints. This abbreviated SAP describes the analyses to be performed.

1.1 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 was planned to enroll approximately 105 subjects (approximately 15 subjects in the run-in [part 1] and 90 subjects in the randomized phase [part 2]).

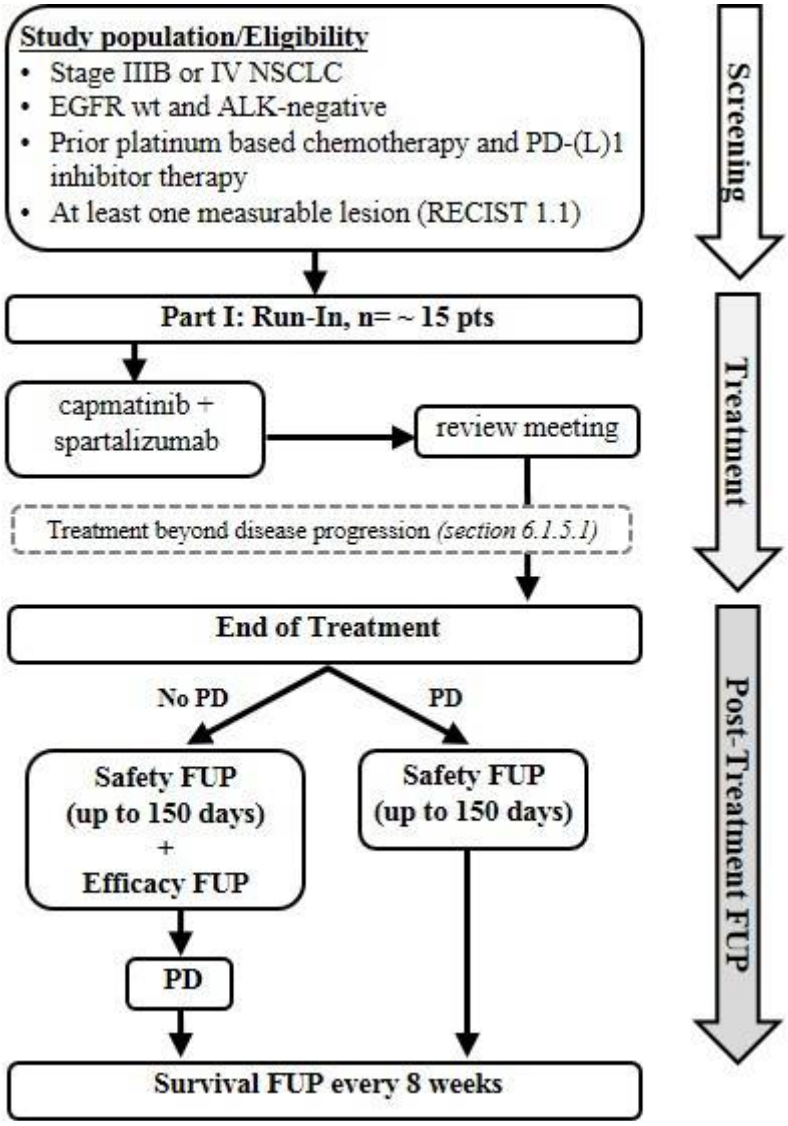
The final analysis results will be summarized in the final abbreviated clinical study report (CSR).

Part 1: Run-in

The primary objective of this part was to assess the safety and tolerability as well as preliminary efficacy of the capmatinib and spartalizumab combination. Eighteen subjects were enrolled and treated with capmatinib and spartalizumab combination. A review meeting took place after all subjects have at least 24 weeks of follow-up.

Refer to Figure 1-1 for an overview of the Part I study design.

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



pts: patients FUP: follow-up

Part 2: Randomized

Based on the preliminary results of the run-in part, the randomized part of the study will not be opened.

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

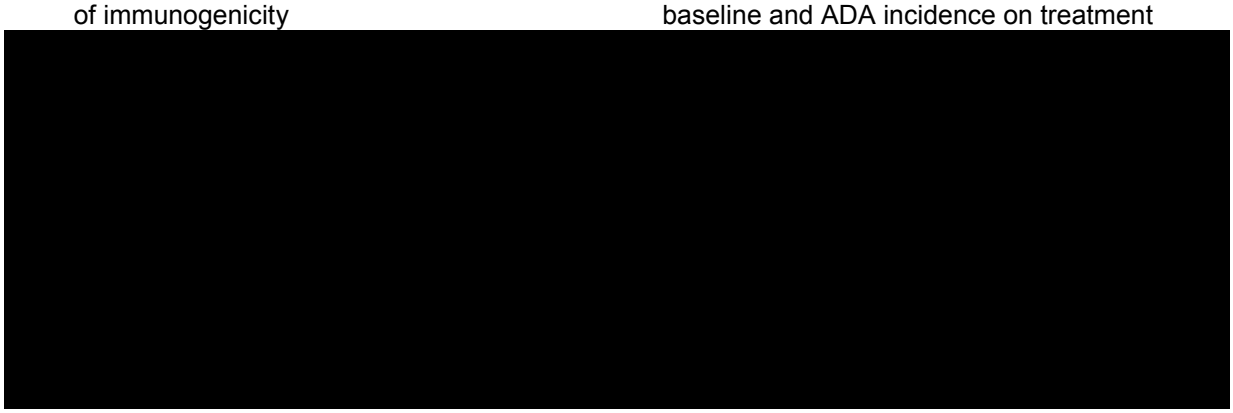
Based on the preliminary results of the run-in part, the randomized part of the study will not be opened.

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below. In consideration of the early permanent recruitment halt and given that the randomized part of the study will not be opened, the final analysis will not be performed as originally planned for all endpoints. This abbreviated SAP describes the analyses to be performed for the run-in part of the study.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Run-in part:** To assess safety and tolerability of capmatinib and spartalizumab combination	• **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:** To assess the overall survival of combination of capmatinib and spartalizumab in comparison to docetaxel	• **Randomized part:** Overall Survival
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• 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 docetaxel	• 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
• To assess the safety profile of capmatinib and spartalizumab combination therapy	• Incidence and severity of AEs and SAEs
• To characterize the pharmacokinetics of capmatinib and spartalizumab as a combination therapy in this patient population	• Pharmacokinetic parameters (e.g. Ctrough, Cmax, AUC)
• To evaluate the prevalence and incidence of immunogenicity	• Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on treatment



Objective(s)	Endpoint(s)
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later and R version 3.2.3 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The analysis cutoff date for the final analysis of study data will be established at the end of the study. All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these cases, the end date will not be imputed and therefore will not appear in the listings.

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.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables ; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group.

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, will refer to capmatinib or spartalizumab. The term investigational drug and study drug are used interchangeably. Whereas, ***study treatment*** will refer to capmatinib in combination with spartalizumab.

Date of first administration of investigational drug

The date of first administration of investigational drug (capmatinib or spartalizumab) is defined as the first date when a non-zero dose of investigational drug (capmatinib or spartalizumab) is administered and recorded on 'Study Treatment: Capmatinib (INC280)' and 'Study Treatment_Infusion_Spartalizumab (PDR001)' (e)CRF pages.

Example: if 1st dose of capmatinib is administered on 05-Jan-2019, and 1st dose of spartalizumab is administered on 03-Jan-2019, then the date of first administration of study drug is on 03-Jan-2019. The date of first administration of study drug will also be referred as start of investigational drug.

Date of last administration of investigational drug

The date of last administration of investigational drug (capmatinib or spartalizumab) is defined as the last date when a nonzero dose of investigational drug (capmatinib or spartalizumab) is administered and recorded on

'Study Treatment: Capmatinib (INC280)' and 'Study Treatment_Infusion_Spartalizumab (PDR001)' (e)CRF pages.

Example: if last dose of capmatinib is administered on 15-Jan-2020, and last dose of spartalizumab is administered on 17-Jan-2020, then the date of last administration of study drug is on 17-Jan-2020. The date of last administration of investigational drug will also be referred as end of investigational drug.

Date of first administration of study treatment

The date of first administration of study treatment is defined as the first date when a non-zero dose of any component of study treatment is administered and recorded on the respective component-specific Study Treatment eCRF.

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a non-zero dose of any component of study treatment was administered and recorded on the respective component-specific Study Treatment eCRF.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date. The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for all assessments (e.g. safety, efficacy, PK, [redacted], etc.) is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.
Note: Some measurements may belong to safety measurement and to efficacy measurement (death' is an efficacy endpoint, but it can also be included in the safety analysis). For safety,the 'study day' will be calculated relative to start of study treatment.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of start of study treatment (for the run-in part) is taken as "baseline" value or "baseline" assessment.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as "baseline" assessment.

In case time of assessment and time of treatment start is captured (e.g. pre-dose ECG), the last available assessment before the treatment start date/time is used for baseline.

For safety parameters (e.g ECGs or vital signs), where study requires multiple replicates per time point, the average of theses measurements would be calculated for baseline (if not already available in the database).

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied:

- If values are from central and local laboratories, the value from central assessment should be considered as baseline.
- If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last value should be considered as baseline.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For adverse event reporting 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 treatment to 150 days after the last dose of spartalizumab, or 30 days after the last dose of capmatinib, whichever is later (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.

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). However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.
Additional summaries will be displayed to report deaths, all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after last administration of spartalizumab or up to 30 days after the last dose of capmatinib whichever comes last.

Note: If a patient starts a post-treatment antineoplastic therapy after the last administration of study treatment, only adverse events suspected to be related to study treatment will be collected up to 150 days after discontinuation of spartalizumab or up to 30 days after discontinuation of capmatinib whichever comes last. All AEs/ all SAEs are planning to be reported up to 150 days after discontinuation of spartalizumab or up to 30 days after discontinuation of capmatinib acknowledging that complete collection of data may not be feasible for each patient.

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-2 Last contact date data sources

Source data	Conditions
Last contact date/last date subject was known to be alive from Survival Follow-up page	Subject status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from study treatment pages	Non-missing dose. Doses of 0 are allowed.
End of treatment date from disposition page at end of treatment	No condition.
Tumor (RECIST / [redacted]) assessment date	Evaluation is marked as 'done'.
Verification for treatment beyond RECIST1.1 PD	At least one non missing parameter value
Laboratory/PK/IG collection dates	Was sample taken? = 'Yes'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the subject was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring if coming from 'Survival information' eCRF.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects in the run-in who received at least one dose of any component of study treatment..

Safety

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). FAS and safety set are the same in the run-in part of this study.

Dose-Determining Set

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.

Pharmacokinetic analysis set (PAS)

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.

Immunogenicity (IG) analysis sets

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.

Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-3.

Table 2-3 Subject classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent	Not applicable
Safety set	No written informed consent	Not applicable
PAS-INC280	No written informed consent	No evaluable capmatinib PK concentration
PAS-PDR001	No written informed consent	No evaluable spartalizumab PK concentration
IG prevalence set	No written informed consent	Subject not in the FAS No determinant baseline IG sample and no determinant post-baseline IG sample
IG incidence set	No written informed consent	Subject not in the FAS No determinant baseline IG sample or no determinant post-baseline IG sample

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

Death events may be used in the analysis if captured from public records (registers), local law and subject informed consent permiting.

Additional data for which there is a separate informed consent, e.g. PK, biomarker etc., collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.1 Subgroup of interest

Not applicable for the run-in part.

2.3 Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries and listings will be reported to assess baseline

comparability. Of note, all patients from the run-in part may be presented in the summaries, if relevant. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. gender, age groups: <65 and ≥ 65 years, race, ethnicity, ECOG performance status, smoking history) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

Body mass index (BMI) (kg/m^2) will be calculated as:

BMI [kg/m^2] = weight[kg] / (height[m]^2) using weight at Baseline.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, details of tumor histology/cytology, histological grade, stage at initial diagnosis, time since initial diagnosis, time from initial diagnosis to first recurrence/progression (in months), time since most recent relapse/progression to start of treatment (in months), stage at time of study entry, presence/absence of target and non-target lesions, number and type of metastatic sites involved. Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on (e) CRF will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC), preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline including source of patient referral and exploratory biomarker informed consent, and treatment beyond progression informed consent will be listed.

2.3.1 Patient disposition

The number (%) of treated patients included in the FAS will be presented overall. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who were treated (*based on the study treatment eCRF pages of each study treatment component completed with non-zero dose administered*)
- Number (%) of patients who are still on-treatment (based on the 'End of Treatment' page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'Disposition' page);
- Reasons for discontinuation from the post-treatment follow-up (based on Study'Disposition');
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment' or 'Disposition'page).

Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the edit checks specification) overall for the FAS. All protocol deviations will be listed.

The outbreak of the Covid-19 pandemic necessitated some changes to the study conduct such that the protocol could not be followed strictly. To understand the effect of the pandemic on the execution and outcome of the study, deviations will be identified and recorded as protocol deviations.

In addition to the pre-defined standard PD terms, Novartis has defined 6 new protocol deviations and the corresponding relationship (health status related vs. site lockdown, patient concerns, etc.) to the COVID-19 pandemic in line with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (March 2020) and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" (April 2020) from EMA as listed below.

- Missing visits
- Changes in procedures and assessments
- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Patient discontinuation due to COVID-19 situation

The COVID-19 related protocol deviations will be summarized if applicable.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized separately for each component of study treatment. Duration of exposure will also be calculated for the study treatment.

Duration of exposure and relative dose intensity will be categorized into time intervals; frequency counts and percentages will be presented for the number(%) of subjects in each interval.

The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized for all subjects. Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to capmatinib and spartalizumab.

Duration of exposure to study treatment (INC280+PDR001) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

The last date of exposure to study treatment (INC280+PDR001) is the latest of the last dates of exposure to capmatinib and spartalizumab (see Table 2-4).

Duration of exposure to study drug (capmatinib/spartalizumab)

Duration of exposure to capmatinib (days) = (last date of exposure to capmatinib) – (date of first administration of capmatinib) + 1.

The last date of exposure to capmatinib is the end date from the last dose administration record non-zero capmatinib dose is recorded in the study treatment eCRF.

Duration of exposure to spartalizumab (days) = (last date of exposure to spartalizumab) – (date of first administration of spartalizumab) + 1.

With:

- The last date of exposure to spartalizumab is the end date from the last dose administration record non-zero spartalizumab dose is recorded in the study treatment eCRF + 27 days (if no death or no lost to follow-up is observed).

- The last date of exposure to spartalizumab is the earliest date among last dose administration record non-zero spartalizumab dose + 27 days and date of death if the subject died.
- The last date of exposure to spartalizumab is the earliest date among last dose administration record non-zero spartalizumab dose + 27 days and date of last contact date if the subject was lost to follow-up.

Note : If the derived last date of exposure goes beyond the data cutoff date, it should be truncated to the date of data cutoff.

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components, respectively.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of study treatment component administration. The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the in the Study treatment – Capmatinib/ Study Treatment_Infusion_Spartalizumab eCRF pages.

For patients who did not take any drug the cumulative dose is by definition equal to zero.

For capmatinib (continuous dosing), the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period. The planned cumulative dose is the planned starting dose summed over the same dosing period.

For spartalizumab (intermittent dosing), the actual cumulative dose should be defined based on the days when the subject is assumed to have taken a non-zero dose during dosing periods (number of infusions taken over the treatment period). The planned cumulative dose is the planned starting dose summed over the number of expected infusions during treatment period (e.g, a subject treated for 60 days is expected to have three infusions).

Planned cumulative dose is calculated as follows:

Spartalizumab in mg	400(mg) * W, where W is the integer part of [duration of exposure (days)/28]
Capmatinib in mg	800 mg/day*d where d is the duration of exposure in days

Dose intensity and relative dose intensity

For dose intensity calculations, the unit of time for capmatinib will be days and for spartalizumab will be cycles.

For capmatinib, the **dose intensity** (DI) is defined as follows:

DI (mg / days) = Actual Cumulative dose (mg) / Duration of exposure to capmatinib (days).

For example:

The duration of exposure is 56 days and the subject received 50 days of full dosing

DI (mg/day) = 40 000 (mg) / 56 (Day) = 714 (mg/day)

For spartalizumab, the **dose intensity** (DI) is defined as follows:

DI (mg / cycles) = length of cycle * (Actual Cumulative dose (mg) / duration of exposure to spartalizumab (days)).

For example:

The duration of exposure is 56 days and the subject received two complete infusions

DI (mg/cycle) = 28 (days) * (800 (mg) / 56 (days)) = 400 (mg/cycle)

For patients who did not take any drug the DI is by definition equal to zero.

For capmatinib, the **Planned dose intensity** (PDI) is defined as follows:

PDI (mg / days) = Planned Cumulative dose (mg) / Duration of exposure to capmatinib (days)

For example:

The duration of exposure is 56 days and the subject is planned to receive 56 days of dosing

PDI (mg/day) = 44 800 (mg) / 56 (Day) = 800 (mg/day)

For capmatinib, the **Planned dose intensity** (PDI) will always be 800 mg/day.

For spartalizumab, the **Planned dose intensity** (PDI) is defined as follows:

PDI (mg / cycles) = length of cycle * (Planned Cumulative dose (mg) / duration of exposure to spartalizumab (days)).

For example:

The duration of exposure is 56 days and the subject is planned to receive two infusions

PDI (mg / cycles) = 28 (days) * (800 (mg) / 56 (days)) = 400 (mg/cycle)

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg / unit of time) / PDI (mg / unit of time)

DI and RDI will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components. RDI will be summarized in percentages. Summary of RDI includes categorical summaries. The RDI categories are < 50%, ≥ 50% - < 75%, ≥ 75% - < 90%, ≥ 90% - < 110% and ≥ 110%.

Dose reductions, interruptions or permanent discontinuations

The number of patients who have dose reductions, interruptions, permanent discontinuations, and the reasons will be summarized separately for each of the study treatment components in the run-in part.

'Dose changed', 'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration Record (DAR) CRF pages will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

Interruption: An interruption is defined as a dose of zero given on one or more days between two non-zero dosing records.

For the purpose of summarizing interruptions and reasons, any two or more consecutive zero doses of capmatinib or spartalizumab will be counted as one interruption if the reasons for these two consecutive dose interruptions are the same. It will be counted as two different interruptions only if the reasons are different. If an interruption occurs for more than one day due to the same reason, but the days are not consecutive, i.e., there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence. For patients who have dose interruption checked but never resume non-zero dose, the dose interruption will not be counted.

Reduction (For Capmatinib only): A dose reduction is defined as a decrease of the total capmatinib daily dose from the protocol planned starting dose (400mg BID) to another non-zero dose or a decrease from the previous non-zero dose that is less than protocol planned starting dose to another non-zero dose, even if the decrease has been directly preceded by an interruption. The number of reductions will be derived programmatically based on the change and the direction of the change.

For example, in the sequence 800 mg total daily to 0 mg to 600 mg to 400 mg, 600 mg and 400 mg total daily will be counted as reductions. On the other hand, if the dose decrease is followed by an interruption, with the dose resuming at the same level prior to the interruption (e.g. in the sequence 800 mg total daily to 600 mg to 0 mg to 600 mg), the second 600 mg will not be counted as dose reduction.

If, due to a dosing error, a patient receives a higher than planned starting dose and moves down to the planned starting dose then this is not considered a dose reduction. However if the dose change is from a higher than planned starting dose down to a lower than protocol planned starting dose, then this is considered a dose reduction. (e.g. in the sequence: 1000 mg total daily to 800 mg total daily to 600 mg total daily, 600 mg is considered as a dose reduction assuming that 800 mg total daily is the protocol planned starting dose).

If a patient receives a lower than previous non-zero dose and resumes later at the protocol specified dose reduction, then the lower dose received due to dosing error and protocol specified dose reduction are dose reductions (e.g. in the sequence: 800 mg daily to 400 mg daily to 600 mg daily, then 400 mg and 600 mg are considered as dose reductions assuming that 800 mg daily is the protocol planned starting dose).

If due to interruption, a patient receives half of the dose during 1 day and followed by an interruption (due to the same reason) then this is not a dose reduction. Dose interruption starts on the day that half of the dose is administered. For example, in the sequence: 800 mg total daily to 400 mg once a day to 0 mg to 600 mg BID, 400 mg is not a dose reduction, 600 mg is a dose reduction.

If due to permanent discontinuation, a patient receives half of the dose the last day of treatment then this is not a dose reduction.

The following are different examples of dose reduction.

Case 1: If a patient did not receive the protocol planned dose for any reason (for e.g. see table below), then this is a dose reduction (e.g. 200/400 mg, 800 mg).

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
[redacted]			400	ONCE PER DAY	DOSING ERROR	**Y**	1st administration different from protocol planned dose (800 mg)
			800	2 TIMES PER DAY			

Case 2: If, due to a dosing error, a patient receives higher than protocol planned dose and moves down to the planned dose then this is not a dose reduction (800 mg, 1000 mg, 800 mg); However if the change is directly from a higher than planned dose down to a lower than protocol planned dose, then this is a dose reduction (e.g. In the sequence, 800 mg, 1000 mg, 400 mg, is a dose reduction).

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
[redacted]			800	2 TIMES PER DAY			
			0		ADVERSE EVENT		
			600	2 TIMES PER DAY	ADVERSE EVENT	Y	
			700	2 TIMES PER DAY	DOSING ERROR	Y	
			800	2 TIMES PER DAY			
			1000	**2 TIMES PER DAY**	**DOSING ERROR**		
			800	**2 TIMES PER DAY**		**N**	moves down to the dose administered just before dosing error
			800	2 TIMES PER DAY			
			0		ADVERSE EVENT		
			600	2 TIMES PER DAY	ADVERSE EVENT	Y	
			700	2 TIMES PER DAY	DOSING ERROR	Y	
			800	2 TIMES PER DAY			
			1000	**2 TIMES PER DAY**	**DOSING ERROR**		
			600	**2 TIMES PER DAY**		**Y**	moves down to a lower dose administered just before dosing error

Case 3: If due to interruption, a patient receives half of the dose during 1 day and followed by an interruption (due to the same reason) then this is not a dose reduction (for ex: 800 mg 2 times per day from [redacted] to [redacted], and 400 mg once per day on [redacted] and then interruption [redacted] to [redacted]). After interruption, dose reduction will be determined using the dose received on a day without interruption (for ex: 600 mg vs 800 mg ignoring 400 mg on [redacted] given it is related to the interruption). The date of [redacted] will be considered a dosing day.

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
[redacted]			800	2 TIMES PER DAY			
			400	**ONCE PER DAY**	**ADVERSE EVENT**	**N**	½ dose for 1 day same reason than interruption Interruption started on [redacted]
			0		**ADVERSE EVENT**		
			600	2 TIMES PER DAY	ADVERSE EVENT	**Y**	Dose reduction from 800 mg to 600 mg [400 mg on 15Jan ignored for reduction determination as part of the interruption]
			0		ADVERSE EVENT		
			800	2 TIMES PER DAY			
			400	ONCE PER DAY	ADVERSE EVENT	N	½ dose for 1 day same reason than interruption Interruption started on [redacted]
			0		ADVERSE EVENT		
			400	ONCE PER DAY	ADVERSE EVENT	Y	Dose reduction from 800 mg to 400 mg [400 mg on [redacted] ignored for reduction determination as part of the interruption]
			800	2 TIMES PER DAY			
			400	ONCE PER DAY	DOSING ERROR	Y	
			800	2 TIMES PER DAY			
			400	**ONCE PER DAY**	**DOSING ERROR**	**Y**	½ dose for 1 day different reason than interruption
			0		**ADVERSE EVENT**		

Case 4: If due to permanent discontinuation, a patient receives half of the dose the last day of treatment then this is not a dose reduction (for ex: 800 mg 2 times per day from [redacted], and 400 mg once per day on [redacted]). This rule is applied for any dose

levels (for ex: 600 mg 2 times per day from [redacted], and 300 mg once per day on [redacted]).

Patient ID	Start date	End date	Dose	Regimen	Reason	Permanently discontinuation	Reduction (derived)
[redacted]			800	2 TIMES PER DAY			
			400	ONCE PER DAY	ADVERSE EVENT	Y	N

2.4.2 Prior, concomitant and post therapies

Prior anti-neoplastic therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized based on FAS. Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

Prior anti-neoplastic medications will be summarized by number of prior regimens of anticancer medications, therapy type, therapy type at last treatment, setting at last treatment, best response to last treatment. Prior antineoplastic medications will also be summarized by ATC class, and preferred term. The medication therapy type of any combination therapy will be classified based on the following order: immunotherapy, chemotherapy, biologic therapy (other than immunotherapy), targeted therapy, hormonal therapy. For example, a combination therapy of chemotherapy and immunotherapy will be classified as 'immunotherapy'.The summary of prior anti-neoplastic radiotherapy will include the radiotherapy locations, (including all locations recorded for each subject), setting at last radiotherapy, and the time (in months) between the last radiotherapy to start of study treatment.

The summary of prior anti-neoplastic surgery will include the time (in months) between the last surgery (non-biopsy procedure) to start of study treatment, procedure at last surgery and residual disease at last surgery.

Anti-neoplastic medications will be coded using the NovDTD/WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD/ NovDTD version will be included in the footnote in the tables/listings.

Post treatment anti-neoplastic therapy

Anti-neoplastic therapies since discontinuation of study treatment-medications will be summarized by ATC class, preferred term, by means of frequency counts and percentages. Antineoplastic radiotherapy (concomitant and since discontinuation of study treatment) will will also be summarized, by means of frequency counts and percentages. Antineoplastic surgery will also be summarized by system organ class and preferred term.

The above analyses will be performed using the FAS.

Concomitant therapy

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. Concomitant medications will be summarized by lowest ATC class and preferred term using frequency counts and percentages.

These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after last dose of capmatinib or 150 days after the last dose of spartalizumab, whichever comes last
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All reported concomitant therapies will be listed.

Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 150 days after the last dose of spartalizumab or 30 days after last dose of capmatinib, whichever comes last, will be flagged in the listing.

The safety set will be used for all concomitant medication tables and listings.

2.5 Analysis of the primary objective

The primary objective is to assess the safety and tolerability of capmatinib and spartalizumab combination

2.5.1 Primary endpoint

Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs, dose interruptions, reductions, and dose intensity.

DLT is defined in the study protocol (See Section 6.5.4, Table 6-6).

2.5.2 Statistical hypothesis, model, and method of analysis

The adaptive BLRM guided by EWOC principle will be used to assess the safety and tolerability of capmatinib (INC280) in combination with spartalizumab (PDR001). The BLRMs will be fitted on the dose-limiting toxicity data (i.e. absence or presence of DLT) during the 56 day DLT window accumulated to model the dose-toxicity relationship.

The dose-toxicity (DLT) relationship is modeled by a 5-parameter BLRM as follows. Let $\pi_1(d_1)$ be the probability of DLT if PDR001 is given as a single-agent at Q4W dose d_1, and $\pi_2(d_2)$ the

probability of DLT if capmatinib is given as a single-agent at total daily dose of d_2. It is assumed that the toxicity of capmatinib is driven primarily by AUC and therefore it is critical to use a total daily dose irrespective of regimen, e.g. 400 mg bid will correspond to 800 mg total daily dose. $\pi_{12}(d_1,d_2)$ denotes the probability of DLT if PDR001 is given in combination with capmatinib at Q4W dose d_1 of PDR001 and total daily dose d_2 of capmatinib. The possibility of synergism or antagonism between the safety profiles of the two drugs is captured in the model of odds of DLT rate with combination doses.

PDR001: $\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

capmatinib: $\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

$\text{Odds}(\pi_{12}(d_1,d_2))) = \pi_{12}(d_1,d_2)/(1- \pi_{12}(d_1,d_2))$

$= \exp(\eta(d_1/d_1^*)(d_2/d_2^*))(\pi_1(d_1)+ \pi_2(d_2) - \pi_1(d_1)\,\pi_2(d_2))/((1- \pi_1(d_1))(1- \pi_2(d_2))),$

where $\text{logit}(\pi.(d.)) = \log[\pi.(d.)/\{1- \pi.(d.)\}]$, $d_1^* = 400$ mg and $d_2^* = 400$ mg are the reference doses of PDR001 and capmatinib respectively, $\alpha_1, \alpha_2, \beta_1, \beta_2 > 0$ and $-\infty < \eta < \infty$ is the interaction coefficient.

The Bayesian approach requires the specification of prior distributions for the model parameters. The prior distributions for the BLRM are derived based on available clinical data on PDR001 (CPDR001X2101) and capmatinib (CINC280X2102 and CINC280C1101). For further details on the BLRM including the prior specification for the model parameters, refer to Appendix 4 of the protocol.

After the run-in part, the posterior distribution for the risk of DLT for new subjects at doses of interest will be evaluated. The posterior distributions 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%]

Dosing decisions are guided by the EWOC principle (Rogatko et al, 2007). A dose may only be used for newly enrolled subjects if the risk of excessive toxicity at that dose is less than 25%. The final estimate of the MTD will also satisfy this criterion.

Listing and summary of DLTs

A summary of the posterior distribution of the model parameters and the posterior distribution of DLT rates based on the DLT data from all subjects included in the DDS will be provided. The corresponding results of the BLRM will also be presented graphically.

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 5.0. The DDS will be used for these summaries.

Safety and Tolerability

See Section 2.8 for details of analysis.

2.5.3 Handling of missing values/censoring/discontinuations

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

2.5.4 Supportive analyses

Not applicable.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives are 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.

2.7.1 Secondary efficacy endpoints

The secondary efficacy endpoints are: 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 as per local investigator's assessment.

Overall Response Rate (ORR)

ORR is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 (see Appendix 1 of the study protocol). The best overall response is the best response recorded using local investigator's review based on RECIST 1.1 from start of treatment until disease progression/recurrence, death, start of new anti-neoplastic therapy, withdrawal of consent or cut-off date, whichever occurs first.

ORR will be calculated based on the FAS using local investigators review of tumor assessment data. Tumor assessments performed before the start of any further anti-neoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR. Localized radiotherapy or limited-field palliative radiotherapy are permitted as per protocol, in which case these should not be considered in determining anti-neoplastic therapy usage.

Disease control rate (DCR)

DCR is defined as the proportion of patients with a best overall response (BOR) of CR or PR, or stable disease (SD) according to RECIST 1.1 criteria. DCR will be calculated using the FAS based on the investigators' tumor assessments.

Progression free survival (PFS)

PFS is defined as the start of treatment to the date of the first documented progression or death due to any cause. PFS will be based on local investigators review of tumor assessments and using RECIST 1.1 criteria.

The analysis will be based on FAS and will include all data observed up-to the cut-off date. If a patient has not progressed or died at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date. PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) will be considered provided tumor assessments continue after initiation of new anti-neoplastic therapy. (See Section 2.7.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment). Discontinuation due to disease progression (collected on the 'disposition' page) without supporting objective evidence satisfying progression criteria per RECIST 1.1 will not be considered disease progression for PFS derivation. Clinical deterioration will not be considered as a qualifying event for progression.

Censoring pattern of PFS

Number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized.

In addition, a summary of reasons for PFS censoring will be provided by dose level based on the following reasons:

1: Ongoing without event
2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: Event after ≥ 2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate TA date and the earliest of the following dates is smaller or equal to interval of 2 missing tumor assessments:

1. Analysis cut-off date,
2. Date of consent withdrawal,
3. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. 'Ongoing',
2. 'Withdrew consent',
3. 'Lost to follow-up',

If the time interval is larger than the interval of 2 missing tumor assessments with no event observed, then the PFS censoring reason will always default to 'Adequate assessment no longer available'. If the time interval between the last adequate tumor assessment date and the PFS

event date is larger than the interval of 2 missing tumor assessments then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

These summaries on censoring reasons will be produced for PFS by investigator.

Duration of response (DOR)

DOR is defined as the time from the date of first documented CR or PR (date of initial response is used, not date of confirmation) to the first documented progression according to RECIST 1.1 based on local investigators review of tumor assessment data or death due to any cause. Patients continuing without progression or death will be censored at the date of their last adequate tumor assessment using the censoring rule described for PFS analysis.

Time to response (TTR)

Time to response (TTR) is defined as the time from the start of treatment (run-in part) to the first documented response of either CR or PR, which must be subsequently confirmed (date of initial response is used, not date of confirmation) using local investigators review of tumor assessment data and according to RECIST 1.1.

All patients in the FAS will be included in the time to response calculation. Patients who did not achieve a confirmed PR or CR will be censored at:

- the maximum follow-up time (i.e. FPFV - LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause);
- the last adequate tumor assessment date for all other patients.

2.7.2 Statistical hypothesis, model, and method of analysis

Response rates

ORR and DCR will be summarized using descriptive statistics (N, %) along with two-sided exact binomial 95% CIs [Clopper and Pearson 1934].

PFS

PFS will be analyzed in the FAS as defined in Section 2.2 and including all data observed up to the cut-off date. The survival distribution of PFS will be estimated using the Kaplan-Meier method. The medians of PFS and 95% confidence intervals of the medians [Brookmeyer and Crowley 1982], along with the proportion of subjects alive at 3, 6 and 9 months and the associated 95% confidence intervals, will be presented. Date of PD, last date free of PD, date of death, principle cause of death and last date know alive for all subjects will be listed.

TTR

TTR will be summarized using the KM method based on FAS only if there are at least 10 subjects with a confirmed BOR of CR and PR. Since there are not enough responses, no summary statistics is applicable. By patient listing will be provided.

DOR

DOR is analyzed based on FAS for patients with confirmed BOR of CR or PR if there are at least 10 subjects with a confirmed BOR of CR and PR . Since there are not enough responses, no summary statistics is applicable. By patient listing will be provided.

2.7.3 Handling of missing values/censoring/discontinuations

PFS

PFS will be censored at the last adequate tumor assessment (TA) if one of the following occurs: absence of event; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a TA not performed or tumor assessment with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more. The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD or non-CR/non-PD before an event or a censoring reason occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the date of start date of study treatment will be used.

Refer to Table 2-5 for censoring and event date options and outcomes for PFS.

Table 2-5 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of start of treatment	Censored
Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Date of last adequate assessment	Censored
New anticancer therapy given prior to protocol defined progression	Ignore the new anticancer therapy and follow situations above	As per above situations
Death before first PD assessment	Date of death	Progressed

ORR

Patients with unknown or missing best overall response (BOR) will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. For the computation of ORR, these patients will be included in the FAS and will be counted as 'failures'.

Of note, patients with only non-measurable disease at baseline are not allowed in the study. However, in case there are such patients, they will be part of the analysis and will be included in the numerator only if a CR was observed (as "responders").

Only tumor assessments performed on or before the start of a new antineoplastic treatment other than study drug(s) (not considering palliative radiotherapy) will be considered in the assessment of BOR.

2.8 Safety analyses

For all safety analyses, the Safety Set will be used.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period. Additional summaries will be displayed to report all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after the last dose of spartalizumab, or 30 days after the last dose of capmatinib, whichever is later (including start and stop dates). All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency.

The following adverse event summaries will be produced: overview of adverse events and deaths (number and % of subjects who died, with any AE, any SAE, any dose reductions/interruptions etc use OSO shell), AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy. In addition, a summary of serious adverse events with number of occurrences will be produced

(an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block; if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

For DLTs, summary will be produced (See Section 2.5).

2.8.1.1 Adverse events of special interest / grouping of AEs

Adverse Events of Special Interest (AESI) consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical or safety interest in connection with the study compound. All definitions of AESI for capmatinib and spartalizumab will be stored in their respective Case Retrieval Strategy (CRS) sheet with clear versioning and reference to the MedDRA version used. If a CRS update is necessary, the final version needs to be available in a reasonable time ahead of the DBL. The CRS version will be included as a footnote of the AESI tables.

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound capmatinib or spartalizumab. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

All AESI definitions or AE grouping are specified in the electronic Case Retrieval Strategy (eCRS), in which they are identified by the flag “SP”. This file may be updated based on review of accumulating trial data, and therefore the groupings are also subject to potential change. The most up-to-date version of the eCRS will be used at the time of the analysis.

For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death, etc.).

If sufficient number of events occurred, analysis of time to first occurrence will be applied. The analysis will be performed for AESI regardless of study drug relationship and for AESI suspected to be study drug related.

Time to first occurrence of an AESI is defined as time from start of study treatment to the date of first occurrence of first event within an AESI, i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1.

In the absence of an event during the on-treatment period, the censoring date applied will be **the earliest** of the following dates:

- death date
- new anticancer antineoplastic therapy start date (not considering palliative radiotherapy),
- end date of on-treatment period
- data cut-off date
- withdrawal of informed consent date.

The corresponding censoring reason will be used: death, new anti cancer therapy, treatment discontinuation, ongoing at cut-off date or consent withdrawal.

Median together with 95% confidence interval as well as 25th percentile and 75th percentile will be presented.

In addition, the median time to occurrence for the subset of subjects who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced for all subjects by system organ class and preferred term. Additional summary will be displayed to report all deaths up to 150 days after the last dose of spartalizumab or up to 30 days after the last dose of capmatinib whichever comes last.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.8.3 Laboratory data

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include only on-treatment assessments (see Section 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (CTC v5.0) regardless of the baseline status. Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT >3×ULN, >5×ULN, >8xULN, >10×ULN, >20×ULN
- AST >3×ULN, >5×ULN, >8×ULN, >10xULN, >20×ULN
- ALT or AST >3×ULN, >5xULN, >8×ULN, >10xULN, >20×ULN
- TBL > 2xULN, >3×ULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3×ULN & TBL > 2×ULN & ALP ≥ 2×ULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

At scheduled visits, triplicate 12-lead ECG's will be performed. ECG machines will automatically calculate heart rate and measures of HR, PR, QRS, QT, QTcB and QTcF intervals. ECG data will be read and interpreted locally.

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.

Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

Data analysis

The number and percentage of patients with notable ECG values will be presented overall and by dose level (if applicable).

- QT, QTcF, QTcB
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.4.2 Vital signs

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

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-6 below.

Table 2-6 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	≥ 180 with increase from baseline of ≥ 20	≤ 90 with decrease from baseline of ≥ 20
Diastolic blood pressure (mmHg)	≥ 105 with increase from baseline of ≥ 15	≤ 50 with decrease from baseline of ≥ 15
Pulse rate (bpm)	≥ 100 with increase from baseline of >25%	≤ 50 with decrease from baseline of > 25%
Body temperature	≥ 39.1	-

The number and percentage of subjects with notable vital sign values (high/low) will be presented. Trends of systolic and diastolic blood pressures over time will be displayed via boxplots for scheduled assessment timepoints along with corresponding tables displaying the statistics used for the box plots.

A listing of all vital sign assessments will be produced and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 ECOG performance status

The ECOG PS scale (Table 2-7 will be used to assess physical health of patients, ranging from 0 (most active) to 5 (least active):

Table 2-7 ECOG Performance Scale

Score	Description
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

Shift tables of ECOG performance status at baseline to worst post-baseline ECOG performance status by score will be provided using the safety set; shift tables of ECOG performance status at baseline to best post-baseline ECOG performance status by score will also be provided. ECOG performance status at each time point will be listed.

2.9 Pharmacokinetic endpoints

The secondary objective for PK is to characterize the pharmacokinetics of capmatinib and spartalizumab as a combination therapy in this patient population

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

PK parameters

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 2-8 except Tmax, where only n, median, minimum and maximum will be presented. Any missing PK parameter data will not to be imputed. All individual PK parameters will be listed using the Pharmacokinetic analysis set.

Table 2-8 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 (lambda_z) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives

PK concentrations

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.

The arithmetic mean (SD) and geometric mean and individual concentration versus time profiles for spartalizumab and capmatinib will be displayed graphically for patients in Pharmacokinetic analysis set on the linear and semi-log view.

All individual plasma for spartalizumab and capmatinib concentration data will be listed for the Full analysis set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

2.10 Immunogenicity and PK/PD analyses

Another secondary objective is to evaluate the prevalence and incidence of immunogenicity.

2.10.1 Immunogenicity

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

2.10.1.1 Sample ADA Status

Each IG sample is assessed in a three tiered anti-drug anti-body (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not subject to a confirmatory assay. Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples identified as positive in the confirmatory assay are considered ADA positive. Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data:

- Result of assay according to pre-specified confirmatory cut point: ADA positive (yes) or ADA negative (no)
- Titer (for positive samples): numerical representation of the magnitude of the ADA response
- Drug tolerance level: highest drug concentration that does not interfere in the ADA detection method
- Fold titer change (i.e. x-fold): threshold for determining treatment boosted

Sample ADA status will be defined for spartalizumab, based on their respective PK concentrations. Sample ADA status is determined based on the following definitions:

- *ADA-inconclusive sample*: Sample where assay is ADA negative and spartalizumab PK concentration at the time of IG sample collection is greater than or equal to the drug tolerance level or missing.
- *Unevaluable sample*: Sample where assay is not available.
- *Determinant sample:* Sample that is neither ADA-inconclusive nor unevaluable.

The following definitions apply only to determinant samples:

- *ADA-negative sample*: Determinant sample where assay is ADA negative and spartalizumab PK concentration at the time of IG sample collection is less than the drug tolerance level.
- *ADA-positive sample*: Determinant sample where assay is ADA positive.

The following definitions apply only to post-baseline ADA-positive samples with a corresponding determinant baseline sample. To be classified as *treatment-boosted* or *treatment-unaffected*, both the post-baseline and baseline titer must be non-missing:

- *treatment-induced ADA-positive sample:* ADA-positive sample post-baseline with ADA-negative sample at baseline.
- *treatment-boosted ADA-positive sample:* ADA-positive sample post-baseline with titer that is at least the fold titer change greater than the ADA-positive baseline titer.
- *treatment-unaffected ADA-positive sample*: ADA-positive sample post-baseline with titer that is less than the fold titer change greater than the ADA-positive baseline titer.

NOTE: PK concentrations which are flagged for exclusion will still be used to determine ADA-inconclusive and ADA-negative samples.

The following summaries of ADA sample status (n and %) will be provided using *Immunogenicity prevalence set*:

- ADA-positive samples (i.e. ADA prevalence) both overall and by time point (including baseline). For summaries by time point, the denominator is the number of subjects at that time point with a determinant sample.

Listings will be provided of sample ADA status (including titer for positive samples).

2.10.1.2 Subject ADA status

Any IG sample collected after 150 days of the last dose of spartalizumab will not be used for summaries or derivations and will only be included in the listing.

Subject ADA status is defined as follows:

- *Treatment-induced ADA-positive subject*: subject with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- *Treatment-boosted ADA-positive subject*: subject with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.
- *Treatment-unaffected ADA-positive subject*: subject with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample.

- *Treatment-reduced ADA-positive subject*: subject with ADA-positive sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *ADA-negative subject*: subject with ADA-negative sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *Inconclusive subject*: subject who does not qualify as treatment-induced ADA-positive, treatment-boosted ADA-positive, treatment-unaffected ADA-positive, treatment-reduced ADA-positive, or ADA-negative.

The following summaries of ADA subject status (n and %) will be provided using *Immunogenicity incidence set*:

- Treatment-boosted ADA-positive subjects; denominator is the number of subjects with ADA-positive sample at baseline.
- Treatment-induced ADA-positive subjects; denominator is the number of subjects with ADA-negative sample at baseline.
- ADA-negative subjects: denominator is the number of subjects in *Immunogenicity incidence set*.
- ADA-positive subjects (i.e. ADA incidence): calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive subjects; denominator is the number of subjects in *Immunogenicity incidence set*.

Listings will be provided of subject ADA status.

2.11 Other Exploratory analyses

Not applicable.

2.12 Interim analysis

Not applicable.

3 Sample size calculation

3.1 Primary analysis

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

3.2 Power for analysis of key secondary variables

Not applicable.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: T-he dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	**Rule**
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days (150 days for PDR001) not > (death date, cut-off date, withdrawl of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment 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 the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. 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.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used should be specified in the footnote of relevant tables.

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

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version v5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.4 Statistical models

Kaplan-Meier estimates

An estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

6 Reference

Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.

Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.

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

Rittmeyer A, Barlesi F, Waterkamp D, et al (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet p. 255-265.