NOVARTIS

Clinical Development

INC280/Capmatinib

CINC280I12201 / NCT04139317

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

Statistical Analysis Plan (SAP)

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21-Sept-2021	Prior to DB lock	Draft v1.0		

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List of tables

List of abbreviations

ADA	Antidrug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BLQ	Below the limit of quantification
BOR	Best overall response
CI	Confidence Interval
CR	Complete Response
CRF	Case Report/Record Form
CRO	Contract research organization
CSR	Clinical Study Report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CV	Coefficient of variation
DAR	Dosage Administration Record
DCR	Disease Control Rate
DI	Dose Intensity
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
FAS	Full Analysis Set
GPS	Global Programming and Statistics
HLGT	High level group term
HLT	High level term
HR	Hazard Ratio
HR2	Hazard ratio after the risk change in the two-piece exponential distributions
IB	Investigators brochure
[redacted]	[redacted]
IG	Immunogenicity
[redacted]	[redacted]

[redacted]	[redacted]
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal Epithelial Transition
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NMQ	Novartis MedDRA querie
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall survival
PAS	Pharmacokinetic analysis set
PD	Protocol Deviations
PDI	Planned Dose Intensity
PD-L1	Programmed death-ligand 1
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PR	Partial Response
PT	Preferred term
RDE	Recommended dose for expansion
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SMQ	Standardized MedDRA querie
SOC	System organ class
TBIL	Total bilirubin
TFL	Tables, Figures and Listings
TPS	Tumor Proportion Score
TTR	Time-to-Response
ULN	Upper limit of normal
WBC	White blood cell

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study INC280I12201 that will be presented in the CSR. The output shells (in-text and post-text) accompanying this document can be found in the TFL shells document. The specifications for derived variable and datasets can be found in the PDS document. This version of the SAP is based on the Protocol Amendment v03 dated 21-Apr-2021.

All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., MTD/RDE declaration, IB updates, abstracts, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

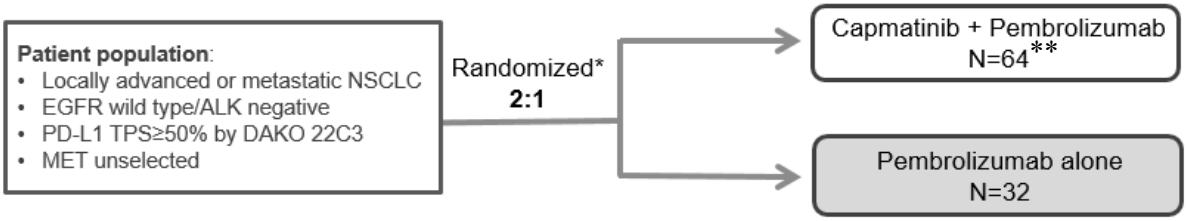
1.1 Study design

This is a randomized, open-label, multicenter, phase II study evaluating the efficacy and safety of capmatinib (INC280) plus pembrolizumab (also referred to as PREMBO in this document) in comparison to pembrolizumab alone as first line treatment for locally advanced or metastatic NSCLC with PD-L1 expression ≥ 50%, MET unselected, EGFR wild type and ALK negative.

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

The enrollment was halt on 21-Jan-2021 due to lack of tolerability observed in the capmatinib plus pembrolizumab arm. Please refer to protocol amemdment 03 for more details.

Figure 1-1 Study Design



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

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

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

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

[redacted]

Objective(s)	Endpoint(s)
[redacted]	

2 Statistical methods

2.1 Data analysis general information

Study data will be analyzed by Novartis personnel and/or designated CRO(s) using the most updated SAS® version in the GPS environment and for the Bayesian modeling and analyses the most updated R version. For analyses using R and/or WinBUGS/JAGS (e.g., Bayesian analysis) the most updated versions in the MODESIM environment will be used. PK parameters may be calculated as applicable using non-compartmental methods available in Phoenix WinNonlin version 5.2 or higher.

The study data will be analyzed and reported based on all subjects' data up to the time when all subjects have completed treatment and safety follow-up period. Data from participating centers in this study protocol will be combined, so that an adequate number of subjects will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and pharmacodynamics measurements using descriptive statistics for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

Unless otherwise specified, data will be presented by treatment arm, as defined below.

- Study arms: INC280 + PEMBRO, PEMBRO alone.

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 subjects 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 subjects 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).

For screen failure subjects, the eCRF data collected will not be included in the analyses, but will be reported in the CSR as separate listings.

2.1.1 General definitions

2.1.1.1 Study drug and study treatment

Investigational drug will refer to either INC280 or PEMBRO. The terms investigational drug and study drug are used interchangeably. Study treatment refers to both INC280 + PEMBRO and PEMBRO alone.

2.1.1.2 Date of first/last administration of study treatment

For PEMBRO single agent treatment, the date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of PEMBRO was administered and recorded on the DAR eCRF.

For INC280 + PEMBRO, the date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of any component of study treatment was administered and recorded on the DAR eCRF.

2.1.1.3 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 safety assessments (e.g., AE onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, etc.) is the start of study treatment. Note, the day of start of study treatment is Day 1, and the day before the date of first study treatment is Day – 1, not Day 0.

The reference start date for all other, non-safety assessments (e.g., tumor assessment, survival time, disease progression, tumor response, ECOG performance status) is the date of randomization.

The study day as well as the reference date (start of study treatment or date of randomization) 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.

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.

2.1.1.4 Baseline

Baseline is the result of an investigation describing the “true” state of the before start of study

treatment administration.

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 these 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.

Laboratory data

If labs with duplicate laboratory measurements taken at the last assessment date on or before the start date of study treatment, then the rule described below will be applied for the calculation of baseline:

- For lab parameters with CTC grade, the lower CTCAE grade will be considered as the baseline value. For lab parameter with a bi-directional CTC grade, two baselines should be created; where the record with grade below 0 should be the baseline of the 'Hypo' parameter, and the other record should be the baseline for the 'Hyper' parameters.
- For non-gradable lab parameters:
  - If both within normal range: take average value.
  - If one within normal range and the other outside: take the one within normal range.
  - If both outside normal range: take the one closest to the normal range.

ECGs

Baseline for ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. Study Day 1 scheduled pre-dose ECGs will be considered to have been obtained prior to study drug administration if dosing time or ECG time is missing.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement. For unscheduled assessments on study Day 1, the assessment is classified as post-baseline.

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

For **efficacy assessments**, the last available assessment, including unscheduled assessments, on or before the date of randomization is taken as "baseline" assessment.

2.1.1.5 On-treatment assessment/event and observation periods

For all safety reporting the overall observation period will be divided into three mutually exclusive segments:

- **pre-treatment period**: from day of subject's informed consent to the day before first administration of study treatment
- **on-treatment period**: from date of first administration of study treatment to 30 days after date of last administration of study treatment (including start and stop dates)
- **post-treatment period**: starting at Day 31 after last administration of study treatment.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

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 AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

2.1.1.6 Last contact date

The last contact date will be derived for subjects not known to have died at the analysis cut-off using the last complete date among the following data sources (Table 2-1).

Table 2-1 Last contact date data sources

Source data	Conditions
Last contact date/last date subject was known to be alive from Survival eCRF page	Patient status is reported to be alive or unknown in the survival eCRF page
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from study treatment eCRF	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor (RECIST) assessment date	Evaluation with a response
Date of verification for treatment beyond RECIST 1.1 Progressive disease.	Will the subject continue treatment beyond disease progression as per RECIST 1.1? marked as 'Yes'
PK collection dates	Was sample taken marked as 'Yes'
Vital signs/ECGs/Laboratory date	At least one non-missing parameter value
Performance Status date	Non-missing performance status

Source data	Conditions
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 DAR) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF.

The last contact date will be used for censoring of subjects in the analysis of OS.

2.2 Analysis Sets

Full Analysis Set (FAS)

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

Safety Set

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

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

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

Pharmacokinetic Analysis Set (PAS) and immunogenicity (IG) set

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

- receive the planned capmatinib treatments prior to sampling
- for INC280 PK samples taken on or after Cycle 2 Day 1, take the same dose of INC280 for at least 3 consecutive days prior to sampling
- (for pre-dose samples) not to vomit within 4 hours after the last dosing of capmatinib prior to sampling; (for post-dose samples) not to vomit within 4 hours after the dosing of capmatinib
- (for pre-dose sample) have the sample collected before the next dose administration and 9-15 hours after the last dose administration.

The PK parameter analysis for the first 8 patients will include all patients who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- patient receives the planned treatments
- patient provides at least one primary PK parameter
- patient did not vomit within 4 hours after the dosing of INC280
- for Cycle 2 Day 1 profile of INC280, patient took the same dose of INC280 for at least 3 consecutive days prior to sampling
- for Cycle 2 Day 1 profile of INC280, patients are required to have the pre-dose sample collected before the next dose administration and at least 9 hours after the last dose administration of INC280.

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

- have received one of the planned pembrolizumab treatments prior to sampling
- (for pre-dose samples) have the sample collected before the next dose administration.

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

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

Note: Some subject's data may not be adequate for the reliable estimation of some PK parameters. These cases will be identified and their PK parameters will be excluded from the relevant summaries. The criteria of exclusion will be listed in Table 2-2.

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

2.2.1 Classification of subjects

Subjects may be excluded from the analysis populations defined above based on the protocol deviations (PDs) entered in the database and/or on specific classification rules defined in Table 2-2.

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

Analysis set	PDs leading to exclusion	Non-PDs to exclusion
Full analysis set (FAS)	No written inform consent	Subject not receiving a dose of study treatment
Safety set	No written inform consent	Subject not receiving a dose of study treatment
INC-PAS and Pembro-PAS	No written inform consent	Subject not receiving a dose of study treatment.

	C1D1 Pembro PK/IG or INC PK/IG sample not collected or collected after dosing	Subject not providing any evaluable PK concentration for capmatinib or Pembro, respectively
Immunogenicity (IG) prevalence set	No written inform consent	Subject not receiving a dose of study treatment Subjects without a determinant baseline IG sample and at least one determinant post-baseline IG sample
Immunogenicity (IG) incidence set	No written inform consent	Subject not receiving a dose of study treatment Subjects without a determinant baseline IG sample or at least one determinant post-baseline IG sample.

2.2.2 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 subject withdraws full consent is recorded in the eCRF.

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 PD criterion.

2.2.3 Subgroup of interest

ORR, DCR and PFS based on local investigator assessment, may be summarized by histological type (squamous vs. non-squamous) in order to examine the homogeneity of treatment effect provided that the primary efficacy analysis based on the FAS is positive.

No formal statistical test of hypotheses will be performed for the subgroup analysis.

ORR and DCR are calculated based on the data from the FAS and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented for each subgroup.

PFS will be summarized using the KM method, based on the FAS. Median PFS, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented for each subgroup if data allows it. KM estimates for PFS proportions at specific timepoints (3, 6, 12, and 18 months), along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided. The number (%) of events and subjects censored will also be summarized by subgroup.

2.3 Subject disposition, demographics and other baseline characteristics

Summaries and listings described in this section will be done by treatment arms based on the FAS.

2.3.1 Subject disposition

The FAS will be used for the subject disposition summary tables and listings. The following will be tabulated:

- Number (%) of subjects randomized/treated;
- Number (%) of subjects who are still on-treatment;
- Number (%) of subjects who discontinued treatment;
- Primary reasons for study treatment discontinuation;
- Number of (%) subjects followed up/not followed after discontinuation of study treatment;
- Number (%) of subjects who discontinued from study;

2.3.2 Basic demographic and background data

Demographic data including age, sex, race, ethnicity, smoking status, baseline weight, baseline height, baseline PD-L1 expression, and ECOG (WHO) performance status will be listed and summarized. Age (18-<65, ≥65 years) categories will be summarized.

2.3.3 Medical History

Medical history and ongoing medical conditions will be summarized by SOC and PT separately and listed, using the latest MedDRA terminology available at the time of reporting.

2.3.4 Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include details of tumor histology/cytology, histologic grade, predominant histology/cytology, additional histology/cytology, staging system, stage at initial diagnosis, stage at study entry, time (in months) since initial diagnosis of primary site, time (in months) from initial diagnosis to first recurrence/relapse, time (in months) since most recent recurrence/relapse, types of lesions (target and non-target lesions) at baseline, current extent of disease (metastatic sites), and PD-L1 expression. Note that PD-L1 information is taken from the clinical database as standard.

Imputation rules for partially missing dates are provided in Section 5.1.3.3.1.

2.3.5 Protocol deviations

The number (%) of subjects in the FAS with any important PD will be tabulated by the deviation category (selection criteria not met; study treatment deviation; not discontinued after meeting withdrawal criteria; use of prohibited concomitant medication; other deviation). The full list of PDs are documented in the Study Specification Document. Important PDs leading to exclusion from analysis sets will be tabulated separately. ALL PDs will be listed.

2.4 Study treatment, rescue medication, other concomitant therapies, compliance

Summaries and listings described in this section will be done by study treatment arms based on the Safety set. Exceptions are specified in each subsection.

2.4.1 Study treatment

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

Duration of exposure will be categorized into time intervals (e.g., <2 wk, 2-<5 wk, 5-<10wk, 10-<20 weeks, +20 weeks); frequency counts and percentages will be presented for the number (%) of subjects in each interval. Continuous summaries for duration of exposure will be provided using weeks as time units.

The duration of exposure to each treatment will be summarized by means of descriptive statistics using the Safety set.

2.4.1.1 Duration of exposure for investigational drug

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

With:

- The first date of exposure for capmatinib is the first date when a non-zero capmatinib dose was administered and recorded on the study treatment eCRF.
- The last date of exposure to capmatinib is the end date from the last DAR when a non-zero capmatinib dose is recorded in the study treatment eCRF.

Duration of exposure to pembro (days) = (last date of exposure to pembro) – (date of first administration of pembro) + 20.

With:

- The first date of exposure for pembro is the first date when a non-zero pembro dose was administered and recorded on the study treatment eCRF.
- The last date of exposure to pembro is the end date from the last DAR when a non-zero pembro dose is recorded in the study treatment eCRF + 20 days (if no death or no lost to follow-up is observed).

Note: if a subject died or was lost to follow-up before the derived last date of exposure, the last date of exposure to study drug/study treatment is the date of death or the date of last contact, respectively. If the derived last date of exposure goes beyond the data cut-off date, it should be truncated to the date of data cut-off.

Definition of date of last contact can be found in Section 2.1.1.6. Summary of duration of exposure of investigational drug will include categorical summaries (based on clinically meaningful time intervals) and continuous summaries (i.e., mean, standard deviation, etc.) using appropriate units of time.

2.4.1.2 Duration of exposure to study treatment

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

The date of first/last exposure to study treatment is defined in Section 2.1.1.2.

2.4.1.3 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 investigational drug 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 study treatment eCRF.

For subjects who did not take any drug, the actual cumulative dose is by definition equal to zero for that drug.

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 pembro (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 63 days is expected to have three infusions).

2.4.1.4 Dose intensity and relative dose intensity

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

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

DI (mg/day) = 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 (days) = 714 (mg/day)

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

DI (mg/cycle) = length of cycle ×(actual cumulative dose (mg) / duration of exposure to pembro (days)).

For example:

The duration of exposure is 63 days and the subject received three complete infusions

DI (mg/cycle) = 21 (days) × (600 (mg) / 63 (days)) = 200 (mg/cycle)

For subjects 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/day) = 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 (days) = 800 (mg/day)

For permbro, the **planned dose intensity** (PDI) is defined as follows:

PDI (mg/cycle) = length of cycle × (planned cumulative dose (mg) / duration of exposure to pembro (days)).

For example:

The duration of exposure is 63 days and the subject is planned to receive three infusions

PDI (mg/cycle) = 21 (days) × (600 (mg)/63 (days)) = 200 (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 will include categorical summaries. The RDI categories are < 50%, ≥ 50% - < 75%, ≥ 75% - < 90%, ≥ 90% - < 110% and ≥ 110%.

2.4.2 Dose reductions, interruptions and permanent discontinuations

The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

The 'Type of change' field from the study treatment CRF pages will be used to determine the dose interruptions. Dose reductions will be derived programmatically using the dosing information as described below.

The corresponding fields 'Reason for change' will be used to summarize the reasons.

A dose change is recorded when 'Dose change' is entered on the 'Type of change' field on the DAR CRF page, where actual dose administered/total daily dose is different from the prescribed dose.

A dose interruption is recorded when 'Dose interruption' is entered on the 'Type of change' field on the DAR CRF page, where dose administered is interrupted.

For the purpose of summarizing interruptions and reasons, cases where multiple entries for interruption are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in the mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Dose reduction (only for capmatinib): A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only the dose change

is collected in the CRF; the number of reductions will be derived programmatically based on the change and the direction of the change.

Dose interruption: Actual dose administered is equal to zero, between the first and last non-zero doses, following a non-zero actual dose administered. Number of dose interruptions and corresponding reason will be summarized.

2.4.3 Concomitant and post therapies

Summaries and listings described in this section will be based on the FAS.

2.4.3.1 Prior anti-neoplastic therapy

All prior anti-neoplastic medication, radiotherapy and surgery will be listed.

The number (%) of subjects who received any prior anti-neoplastic medication, radiotherapy or surgery will be summarized.

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), therapy type at last treatment, setting at last treatment. Prior anti-neoplastic medications will also be summarized by ATC class, and PT.

The summary of prior anti-neoplastic radiotherapy will include the radiotherapy locations, (including all locations recorded for each subject), setting at last radiotherapy, and best response at last radiotherapy.

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

Imputation rules for partially missing dates are provided in Section 5.1.3.1.

2.4.3.2 Post treatment anti-neoplastic therapy

Anti-neoplastic therapies (medications, radiotherapies and surgeries) since discontinuation of study treatment will be listed.

2.4.3.3 Concomitant therapies

Concomitant therapies are defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a subject 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 listed by subject and summarized by ATC class and treatment arm.

The summaries will include:

- Medications starting on or after the start of study treatment but no later than 30 days after last dose of study treatment and
- Medications starting prior to start of study treatment and continuing after the start of study treatment.

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date. No imputation will be performed for concomitant medication end dates.

2.4.4 Compliance

Compliance to the study drug is presented by the number of dose reductions and dose interruptions, and the reasons. Subject level listings of all doses administered on-treatment along with dose change reasons will be produced.

2.5 Analysis of the primary objective

The primary endpoint of this study is the PFS. Estimation of PFS will be provided by treatment arm, and will be analyzed based on the FAS population.

2.5.1 Definition of primary endpoint

PFS is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed via local review according to RECIST 1.1.

2.5.2 Statistical hypothesis, model, and method of analysis

Due to the study enrolment halt on 21-Jan-2021, the discontinuation of capmatinib in the combination arm and the stopping of efficacy data collection in the eCRF, the initially planned Bayesian PFS analyses for the primary endpoint will become uninterpretable and this study is no longer expected to meet its primary endpoint. As mentioned in Section 12.8 of the current protocol, the Bayesian model will not be performed and the primary endpoint will be summarized instead using KM curves for PFS for each treatment arm. The FAS will be used. Median PFS, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for PFS proportions at specific timepoints (3, 6, 12, and 18 months), along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided. The number (%) of events and subjects censored will also be summarized.

2.5.3 Handling of missing values/censoring/discontinuations

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

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

2.5.4 Supportive analyses

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

2.6 Analysis of key secondary objectives

Not applicable.

2.7 Analysis of secondary objectives

2.7.1 Secondary endpoints

The secondary efficacy endpoints are ORR, DCR, TTR, DOR as per RECIST 1.1 and OS. Estimation of all secondary endpoints will be provided by treatment arms based on the FAS. All relative listings, tables and figures will be presented by treatment arm, unless otherwise specified.

Objective response rate (ORR)

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

BOR is defined as the best response recorded from the start of the treatment until disease progression/recurrence as per local review and according to RECIST 1.1.

Disease control rate (DCR)

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

Time to response (TTR)

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

Duration of response (DOR)

DOR is defined as the time between the date of first documented response (CR or PR) and the date of first documented progression or death due to underlying cancer.

Overall survival (OS)

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

2.7.2 Statistical hypothesis, model, and method of analysis

No statistical hypothesis was made on secondary endpoints.

Regarding ORR and DCR:

ORR and DCR will be presented by treatment arm, along with their accompanying 95% Clopper-Pearson CI based on the exact binomial distribution (Clopper and Pearson 1934). Individual lesion measurements, overall response assessments per RECIST 1.1 as well as BOR will be listed by subject and assessment date.

Any subsequent tumor assessment after the date of sponsor's decision to discontinue capmatinib (applicable only to subjects on the combination arm), will be excluded from the BOR derivation. In addition, to explore the potential lasting effect of capmatinib, a supportive analysis of BOR will be performed with including tumor assessments after sponsor's decision to discontinue capmatinib.

Regarding DOR, TTR, and OS:

TTR, DOR and OS will be summarized by treatment arms using the KM estimators for the medians along with their accompanying 95% CIs, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997). KM estimates for TTR and DOR at timepoints (3, 6, 12, and 18 months), and KM estimates for OS at timepoints (6, 12, 18 and 24 months), along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided. The number (%) of events and subjects censored will also be summarized. KM curves will be provided as well.

DOR only applies to subjects for whom BOR is CR or PR. The remaining subjects will not be taken into account in the estimation of this endpoint. If there are at least 10 subjects with a confirmed BOR of CR or PR, the KM analysis will be conducted by treatment arm. In addition, descriptive summary statistics of DOR on responders (e.g., subjects achiving at least once CR or PR) only will also be presented. DOR will be categorized into time intervals (e.g., ≤3 months, >3 – ≤6 months, >6 - ≤12 months, >12 months) and frequency counts and percentages will be presented for the number (%) of subjects in each interval. In addition, for the following cumulative categories (e.g., ≥3months, ≥6 months, ≥12 months), frequency counts and percentages will be presented for the number (%) of subjects in each category.

2.7.3 Handling of missing values/censoring/discontinuations

Regarding ORR:

- Subjects in the FAS with unknown BOR will be noted as such in the appropriate tables/listings and counted as non-responders in the ORR calculation.
- If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the BOR must be "Unknown" unless progression or death is reported.
- If any new anti-neoplastic therapy is taken while on study, any subsequent assessments would be excluded from the BOR derivation.

- Confirmed PR or CR reported prior to any additional anticancer therapy will be considered as responses in the calculation of the ORR irrespective of the number of missed assessments before response.

Regarding DOR:

- If progression or death due to any reasons has not occurred by the date of the cut-off, then the subject will be censored following the same rules defined for PFS in Section 2.5.3.
- If a subject with a CR or PR has no progression or death, the subject is censored at the date of last adequate tumor assessment.

Regarding OS:

- The last date the subject was known to be alive is the last date the subject was contacted or seen by the treating team. If no post-baseline dates are available (before death or a censoring reason occurred), the date of randomization will be used.
- If a subject is not known to have died by the date of the cut-off, OS will be censored at the last date the subject was known to be alive.

2.8 Safety analyses

The Safety set will be used for summaries and listings of safety data.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs, (e.g., AE relationship to study drug, AE outcome, etc.). AEs starting during the post-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE in each primary SOC and for each 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 PT 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 by primary SOC and PT, the primary SOC will be presented alphabetically and the PT will be sorted within primary SOC in descending frequency. Tables by either primary SOC or PT will be sorted in descending frequency.

The following AE summaries will be produced for all subjects:

- Overview of AEs summarized by relationship and deaths (number and % of subjects who died, with any AE, any SAE, fatal SAEs, AEs leading to dose reduction/interruptions, AE leading to treatment discontinuation, AEs requiring concomitant or additional treatment);
- AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment);
- SAEs summarized by relationship (all SAEs and SAEs related to study treatment) and severity;
- AEs leading to treatment discontinuation (all AEs and AEs related to study treatment);

- AEs leading to study treatment dose reduction/interruption (all AEs and AEs related to study treatment);
- AEs requiring concomitant or additional treatment (all AEs and AEs related to study treatment);
- SAEs leading to fatal outcome (all SAEs and SAEs related to study treatment).

The following listings will be produced:

- All AEs (Safety set)
- AEs among subjects who were not treated (screening failure subjects)

The following summaries will be produced for all AEs observed (starting or worsening) during the on-treatment and/or post-treatment periods:

- AEs related to study treatment by SOC and PT;
- SAEs related to study treatment by SOC and PT

2.8.2 Deaths

Separate summaries for on-treatment deaths will be produced by treatment arm, SOC and PT.

All deaths will be listed for the Safety set and post-treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects, if any.

2.8.3 EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on on-treatment/treatment-emergent AEs which are not serious AEs with an incidence greater than 5% and on on-treatment/treatment-emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the Safety set population.

If for a same subject, 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.

2.8.4 Adverse events of special interest / grouping of AEs

An AESI is a grouping of AEs that are of scientific and medical concern specific to compound INC280. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLTs (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. Pre-defined AESIs for the current study are as follows:

- Hepatotoxicity
- Central nervous system (CNS) toxicity
- Interstitial Lung Disease and Pneumonitis
- QTc interval prolongation
- Pancreatitis
- Drug-drug interactions with strong CYP3A4 inducers
- Teratogenicity
- Renal dysfunction
- Photosensitivity

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

Summaries of these AESIs will be provided by treatment arm (INC280 + PEMBRO and PEMBRO alone). A listing of all grouping levels down to the MedDRA PTs used to define each AESI will be generated.

Note: From the eCRS, only risk where “Core Safety Risk” = Y should be selected to report AESI in the CSR (the variable name in GPS, for “Core Safety Risk”, is “SP ”).

2.8.5 Laboratory data

2.8.5.1 CTC grading for laboratory parameters

Grade categorization of lab values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of laboratory CTC grades will be based on the observed laboratory values only; clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC 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 version 5.0, 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 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

2.8.5.2 Data analysis

The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1.5).

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

- Worst post-baseline CTC grade (regardless of the baseline status). Each 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:

- Listing of all CTC grade 3 or 4 laboratory toxicities.

Liver function parameters

Liver function parameters of interest are TBIL, ALT, AST and ALP.

The number (%) of subjects with worst post-baseline values will be summarized:

- ALT or AST > 3×ULN
- ALT or AST > 5×ULN
- ALT or AST > 8×ULN
- ALT or AST > 10×ULN
- ALT or AST > 20×ULN
- TBIL > 2×ULN
- TBIL > 3×ULN
- ALT or AST > 3×ULN & TBIL > 2×ULN
- ALT or AST > 3×ULN & TBIL > 2×ULN & ALP < 2×ULN *(*potential Hy's law).

Potential Hy's Law events are defined as those subjects with concurrent occurrence of AST or ALT > 3×ULN and TBIL > 2×ULN and ALP < 2×ULN in the same assessment sample during the on-treatment period. Further medical review has to be conducted to assess potential confounding factor such as liver metastases, liver function at baseline, etc.

2.8.6 Other safety data

2.8.6.1 ECG and cardiac imaging data

The average of the replicates of the ECG parameters at each assessment should be used in the analyses.

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

The number and percentage of subjects with notable ECG values will be presented.

- QT and QTcF
  - New value of > 450 ms and ≤ 480 ms
  - New value of > 480 ms and ≤ 500 ms
  - New value of > 500 ms
  - Increase from baseline of > 30 ms to ≤ 60 ms
  - Increase from baseline of > 60 ms
- Hearth rate
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR-interval
  - 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 by treatment arm and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.6.2 Vital signs

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

Vital signs collected during on-treatment will be summarized. A listing of subjects with notable vital signs will be provided and values measured during the post-treatment follow up will be flagged in the listing. The number and percentage of subjects with notable vital sign values (high/low) will be presented by treatment arm.

Table 2-3 Criteria for notable vital sign values

Vital sign (unit)	Notable high value	Notable low value
Weight (kg)	increase ≥10% from baseline	decrease ≥10% from baseline
Systolic blood pressure (mmHg)	≥180 and increase from baseline of >=20	≤90 and decrease from baseline of ≥20
Diastolic blood pressure (mmHg)	≥105 and increase from baseline of >=15	≤50 and decrease from baseline of ≥15
Heart rate (bpm)	≥100 and increase from baseline of >25%	≤50 and decrease from baseline of >25%
Body temperature (°C)	≥39.1	--

2.9 Pharmacokinetic analysis

All PK analyses will be performed for INC280 and pembrolizumab based on the PAS. PK parameters will be determined by non-compartmental method(s) using the PK profile of capmatinib. For Capmatinib, PK parameters will be derived and reported, when feasible include but may be not limited to those listed in Table 2-4. For pembrolizumab, PK parameters to be reported will include but may not be limited to Ctrough.

Table 2-4 Non-compartmental pharmacokinetic parameters

PK parameter	Definition
AUClast	The AUC from time zero to the last measurable analyte (capmatinib or pembrolizumab) concentration sampling time (tlast) (mass × time × volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount × time × volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass × volume-1)
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 (λz) of a semi logarithmic concentration-time curve (hr). Use qualifier for other half lives.
CL/F	The apparent total body clearance of drug from the plasma (L/hr)
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (L)

2.9.1 Data handling principles

All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of PK parameters, unless otherwise stated under the PAS.

At the time of analysis, concentration data from subjects may be removed from the estimation of certain PK parameters depending on the number of available blood samples, concomitant medications, vomiting, etc. Specific time points might be removed from the analysis set if technical issues with the sample are reported (e.g., sampling issues, missing information). These subjects and concentration data points will be identified at the time of analysis.

2.9.2 Data analysis set

All PK data analyses and PK summary statistics will be based on the PAS (details in section 2.2). Only PK blood samples with date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses.

2.9.3 Basic tables, figures, and listing

Descriptive statistics will be presented for all PK parameters (Table 2-5), as described below.

Table 2-5 Descriptive analysis

Parameters	Descriptive statistics

AUC[1] , C_{max}, C_{trough}, CL/F, $T_{1/2}$, Vz/F	Mean standard deviation, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum.
T_{max}	Median, minimum, and maximum.

[1] Includes all AUC parameters
CV% = standard deviation/mean×100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)×100

Zero concentrations will not be included in the geometric mean calculations. Tmax will be summarized in terms of median values and ranges. Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

A listing of derived PK parameters per subject will be produced by treatment arm.

Analysis of drug concentrations

Descriptive statistics for drug concentrations, including n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum, will be presented at each scheduled time point by treatment. Zero concentrations will not be included in the geometric mean calculation.

The mean (+/- SD) and geometric mean concentration-time profiles of Capmatinib on C2D1 will be displayed graphically on the linear and semi-log view.

2.10 Immunogenicityand PK/Pharmacodynamics analyses

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

2.10.1 Immunogenicity

2.10.1.1 Sample ADA status

Each IG sample is assessed in a three tiered ADA testing approach. All IG samples are analyzed in the initial screening assay (first tier). Only samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for pembrolizumab (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples can test negative in either the screening or confirmatory assay but for analysis purposes they will not be 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 ADA response
- Fold titer change (i.e., x-fold): threshold for determining treatment boosted.

Sample ADA status is determined based on the following definitions:

- 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 pembrolizumab 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 x 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 x fold titer change greater than the ADA-positive baseline titer.

NOTE: The fold titer change is provided in the method validation report by Drug Metabolism & PharmacoKinetics (DMPK) and it is described in the bioanalytical data report.

The following summaries of sample ADA status (n and %) will be provided using IG 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 more than 150 days of the last dose of pembrolizumab will not be used for summaries or derivations and will only be included in the listing.

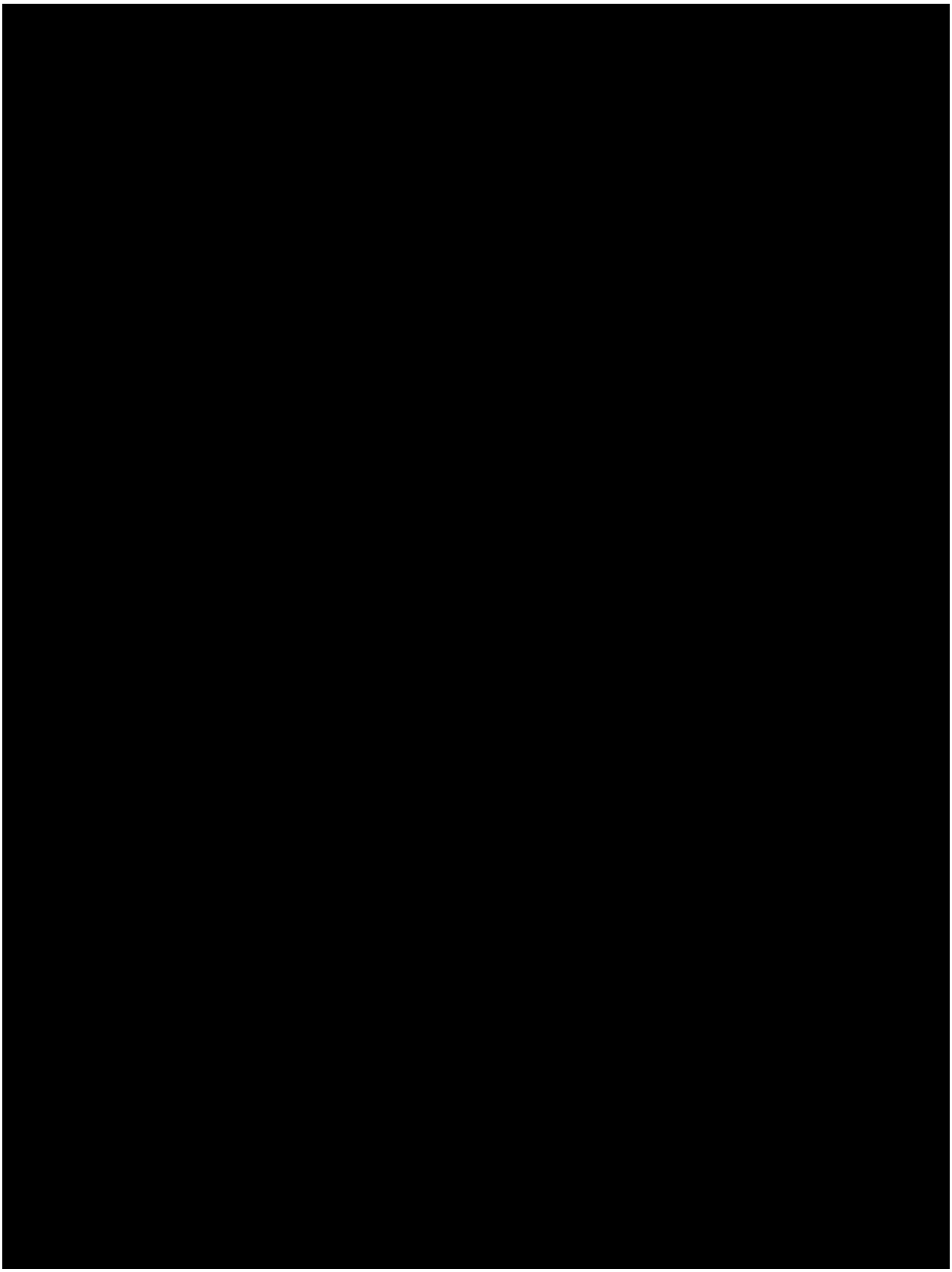
Subject ADA status is defined as follows:

- 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 subject ADA status (n and %) will be provided using IG 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 IG 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 IG incidence set.

Listings will be provided of subject ADA status.



[redacted]

2.13 Interim analysis

An administrative efficacy interim analysis was planned to be conducted by an independent statistician and an independent programmer supporting the DMC, when approximately 30 PFS events have been observed. Results were planned to be reviewed by the DMC and then shared with a Novartis Committee (independent to the study team) in order to make development decisions for other or future studies. The aggregated safety data was planned to be monitored on a regular basis by the DMC (as defined in Section 10.2.1 of the protocol).

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

3 Sample size calculation

Sample size calculation was based on simulations for various scenarios on-treatment outcome, number of subjects included, number of events at the time-point of the primary analysis using the Bayesian model defined in protocol Section 16.3, which will no longer be performed.

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

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

- At least 50% confidence level that HR2 $\leq$0.7
- At least 90% confidence level that HR2<1

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

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

The reported median PFS for pembrolizumab alone as first-line therapy for NSCLC subjects with PD-L1$\geq$ 50% was 10.3 months in KEYNOTE-024 study (Reck et al 2016) and 7.1 months

in KEYNOTE-042 (Mok et al 2019). It is therefore reasonable to assume that the median PFS of pembrolizumab is between 7.1 and 10.3 months. We expect around 50% reduction in the HR2 of PFS in capmatinib plus pembrolizumab, after the time-point of risk change in the assumed two-piece exponential distributions.

Table 3-1 presents the operating characteristics of the Bayesian model with different outcome scenarios keeping stable the total sample size (96 subjects) and the number of total PFS events (50) required at the time-point of the primary analysis. With this combination reasonable operating characteristics can be achieved. Description of operating characteristics of alternative sample size can be found in Section 16.3 of the protocol.

Table 3-1 Operating characteristics for scenarios with 96 subjects and 50 events at the primary analysis

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

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

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

5.1.1.1 Data Imputation for the last administration

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

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page, the subject is considered as on-going:

The subject should be considered as on-treatment. In this case, the cut-off date should be used as the last dosing date for exposure calculations.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT visit 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 the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT visit:

Use last day of the Month (mm).

After imputation, compare the imputed date with the start date of that specific record, if the imputed date is < start date of that record

Use the start date of that record.

Subjects with missing start dates are to be considered missing for all study treatment component related calculations described in Section 2.5.1 and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.1.2 Data Imputation of the first administration

Subjects with missing start dates are generally considered missing for all study treatment component related calculations described in Section 2.5.1 and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.2 AE date imputation

A missing AE start date will be imputed using the logic matrix described in Table 5-1.

Table 5-1 Imputation rules for a partially missing AE start date

	AEM missing	AEM<TRTM	AEM=TRTM	AEM>TRTM
AEY missing	Not imputation	Not imputation	Not imputation	Not imputation
AEY<TRTY	(D)	(C)	(C)	(C)
AEY=TRTY	(B)	(C)	(B)	(A)
AEY>TRTY	(E)	(A)	(A)	(A)

AEM=Month AE started, AEY=Year AE started
TRTM=Month treatment started, TRTY=Year treatment started

Table 5-2 is the legend to the logic matrix shown in Table 5-1 and details the relationship of AE start date to study treatment start date.

Table 5-2 Imputation legend and AE/treatment start date relationship

AE start date relationship	Imputation
(A) After treatment start or uncertain	MAX(01MMMYYYY, TRTSDT+1)
(B) Uncertain	TRTSDT+1

AE start date relationship	Imputation
(C) Before treatment start	15MMMYYYY
(D) Before treatment start	01JULYYYY
(E) After treatment start	01JANYYYY

Before treatment start: Partial date indicates AE start date is prior to treatment start date.
After treatment start: Partial date indicates AE start date is after treatment start date.
Uncertain: Partial date insufficient to determine relationship of AE start date to treatment start date.

No imputation will be performed for missing/incomplete AE end dates. AE with uncertain relationship will be considered as on-treatment AE.

5.1.3 Concomitant medication date imputation

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.1.2). No imputation will be performed for concomitant medication end dates.

5.1.3.1 Prior therapies date imputation

Start date

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that scenario (B) will be replaced to be 'start date of study treatment - 1' (see Section 5.1.2).

End date

Imputed date = min (start date of study treatment, last day of the month), if day is missing;

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.1.3.2 Post therapies date imputation

Start date

Imputed date = max (End of Treatment date + 1, first day of the month), if day is missing;

Imputed date = max (End of Treatment date + 1, 01JAN), if day and month are missing.

Imputed date = End of treatment date +1, if the date is completely missing.

End date

No imputation

5.1.3.3 Other imputations

5.1.3.3.1 Diagnostic and extent of cancer

When a date is recorded as a partial date, the missing day is imputed to the 15th of the month (e.g., DEC2007 imputed to 15DEC2007), and if the day and month are both missing then to 1st of July of that year (e.g., 2007 imputed to 01JUL2007). Such imputed data will be flagged in the listings.

5.2 AEs coding/grading

AEs are coded using the MedDRA terminology. AEs will be assessed according to the 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

5.3.1 CTC grading for laboratory parameters

Grade categorization of lab values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters (see Table 5-3). 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 version 5.0, results will be graded by the low/normal/high 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 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

5.3.1.1 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.

Table 5-3 CTC grades v5.0 for laboratory values in Novartis Oncology

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓ WBC (Leukocytosis)	10^9/L 10^9/L	WBC WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9 /L -	< 3.0 – 2.0 x 10^9 /L -	< 2.0 – 1.0 x 10^9 /L > 100 x 10^9 /L	< 1.0 x 10^9 /L -
Hemoglobin (Anemia) Hemoglobin ↑	g/L g/L	HGB HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M) *(16.113 x mmol/L = g/L)*	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L Increase >0-20 g/L above ULN	< 100 - 80 g/L < 6.2 - 4.9 mmol/L Increase >20-40 g/L above ULN	< 80 g/L < 4.9 mmol/L Increase >40 g/L above ULN	- -
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9 /L
Neutrophils ↓	10^9/L	NEUT		≥2x10^9 /L	< 2.0 - 1.5 x 10^9 /L	< 1.5 - 1.0 x 10^9 /L	< 1.0 - 0.5 x 10^9 /L	< 0.5 x 10^9 /L
Lymphocytes ↓ Lymphocytes ↑	10^9/L 10^9/L	LYM LYM		≥1.5x10^9 /L	< 1.5 - 0.8 x 10^9 /L -	< 0.8 - 0.5 x 10^9 /L > 4 - 20 x 10^9 /L	< 0.5 - 0.2 x 10^9 /L > 20 x 10^9 /L	< 0.2 x 10^9 /L -
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine ↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase ↑	U/L	CK	**30 – 170 U/L** or 0.5 – 2.83 ukat/L (60xukat/L=U/L)	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Albumin (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Calcium (corrected) (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [2] (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Coagulation								
INR ↑	1	INR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time ↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria, e.g., if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN. **Life-threatening consequences and/or hospitalization are not considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either. Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, ≥ **1.5 x 10^9 /L (lymphocytes) and** ≥ **2 x 10^9 /L (neutrophils) are considered as LAB CTC grade 0.** For Creatinine and Fibrinogen, the **comparison with baseline is not considered** for derivation of LAB CTC grades.

6 Reference

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