NOVARTIS

Clinical Development

INC280/Capmatinib/Tabrecta®

CINC280L12301 / NCT04816214

A phase III randomized, controlled, open-label, multicenter, global study of capmatinib in combination with osimertinib versus platinum - pemetrexed based doublet chemotherapy in patients with locally advanced or metastatic NSCLC harboring EGFR activating mutations who have progressed on prior 1st / 2nd generation EGFR-TKI or osimertinib therapy and whose tumors are T790M mutation negative and harbor MET amplification (GEOMETRY-E)

Statistical Analysis Plan (SAP)

Author:

Document type: SAP Amendment

Document status: Final 1.0

Release date: 26-Sep-2022

Number of pages: 45

Template Version 4.0, Effective from 23-Apr-2021

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
10-Aug-2021	Prior to DB lock	Creation of final version	N/A - First version	NA
26-Sep-2022	Prior to DB lock for close-out CSR	Decision to terminate the study early and not open the randomized part	Only a final synoptic CSR will be prepared as an abbreviated report based on the data from run-in part with reduced analyses.	Abbreviate sections 1.1 Study Design, 2.1 Data analysis general information, 2.2 Analysis sets, 2.3.2 Demographics, 2.4 Treatments, 2.5 Analysis supporting primary objective(s), 2.6 Analysis supporting secondary objective(s), 2.7.4 Other safety data, 2.8 Pharmacokinetic endpoints, 5.5 Appendix for Statistical models, 6 Reference; Remove contents for sections 2.10 Patient-reported outcomes, [redacted] 2.13 Interim analysis, 3 Sample size calculation, 4 Change to protocol specified analyses.

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ATC	Anatomical Therapeutic Chemical
AST	Aspartate transaminase
AUC	Area under curve
b.i.d.	bis in die/twice a day
BILI	Total Bilirubin
BIRC	Blinded Independent Review Committee
BOR	Best Overall Response
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria Adverse Event
[redacted]	[redacted]
CV	coefficient of variation
DCR	Disease Control Rate
DDS	Dose-Determination Set
DI	Dose Intensity
DL	Dose Level
DLT	Dose Limiting Toxicity
DOIR	Duration Of Intracranial Response
DOR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eCRS	Electronic Case Retrieval Strategy
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
EOT	End Of Treatment
EQ-5D-5L	EuroQoL-5 Dimension-5 Level
FAS	Full Analysis Set
FBrSI	Fact Brain Symptom index
FPFV	First Patient First Visit
HGRAC	Human Genetic Resource Administration of China
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form

IDCR	Intracranial disease control rate
KM	Kaplan-Meier
LLOQ	lower limit of quantification
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MET	Mesenchymal-to-Epithelial Transition factor
mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small-cell lung cancer
OIRR	Overall Intracranial Response Rate
ORR	Overall Response Rate
OS	Overall survival
PAS	Pharmacokinetic Analysis Set
PD	Progressive disease
PDI	Planned Dose Intensity
PFS	Progression free survival
PFS2	Progression-Free Survival after next line of treatment
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred term
[redacted]	[redacted]
QTcF	Fridericia QT correction formula
RANO	Response assessment in neuro-oncology
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
SOCs	System Organ Classes
TKI	Tyrosine Kinase Inhibitors
TTIR	Time To Intracranial Response
TTR	Time To Response
ULN	upper limit of normal
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report(s) (CSR) of study CINC280L12301, a phase III randomized, controlled, open-label, multicenter, global study of capmatinib in combination with osimertinib versus platinum - pemetrexed based doublet chemotherapy in participants with locally advanced or metastatic NSCLC harboring EGFR activating mutations who have progressed on prior 1st/2nd generation EGFR-TKI, osimertinib or other 3rd generation EGFR-TKI therapy used per local standard of care and whose tumors are T790M mutation negative and harbor MET amplification (GEOMETRY-E).

The content of this SAP is based on the protocol version 01. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock.

Due to the changes of the treatment landscape which have heavily impacted the enrollment of new subjects in the study, the study was closed prematurely after thorough and careful assessment of the study enrollment status and projected timelines for completing enrollment in a timely manner. Consequently, the enrollment for the run-in part was halted on May 18th 2022, and the randomized part of the study will not be opened.

In consideration of the early termination 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 multicenter, open-label, randomized, active-controlled, global phase III study that will enroll adult participants with locally advanced or metastatic NSCLC with EGFR activating mutation, T790M negative, MET amplified who have progressed following EGFR TKIs (EGFR TKIs can be 1st/2nd generation EGFR TKIs, osimertinib or other 3rd generation EGFR TKIs used per local standard care). Randomization of participants who have progressed on prior line with osimertinib will be approximately 50% to 60 % of the planned total number of participants, while for the other third generation EGFR TKI will be maximum of 10% of the planned total number of participants.

The study will consist of an initial safety run-in part to evaluate the safety and tolerability of capmatinib in combination with osimertinib and to confirm the recommended dose for the randomized part, and a randomized part that will evaluate the efficacy and safety of capmatinib in combination with osimertinib compared to platinum (cisplatin or carboplatin) - pemetrexed doublet based chemotherapy as second line treatment.

The study will enroll approximately 10 to 20 participants in the run-in part and 225 participants in the randomized part. Participant's respective treatment (either with capmatinib in combination with osimertinib, or with platinum (cisplatin or carboplatin) - pemetrexed based doublet chemotherapy) will be continued until participant experiences any of the following: documented disease progression by RECIST 1.1 (as assessed by the investigator in the run-in part, and as assessed by the investigator confirmed by BIRC in the randomization part), withdrawal of consent, pregnancy, lost to follow-up, death etc. (futher details in study protocol section 9.1.1).

For all participants, the respective treatment may be continued beyond initial disease progression as per RECIST 1.1, if, in the judgement of the investigator, there is evidence of clinical benefit, and the participant wishes to continue on the study treatment.

After treatment discontinuation, all participants will be followed for safety evaluations during the safety follow-up period.

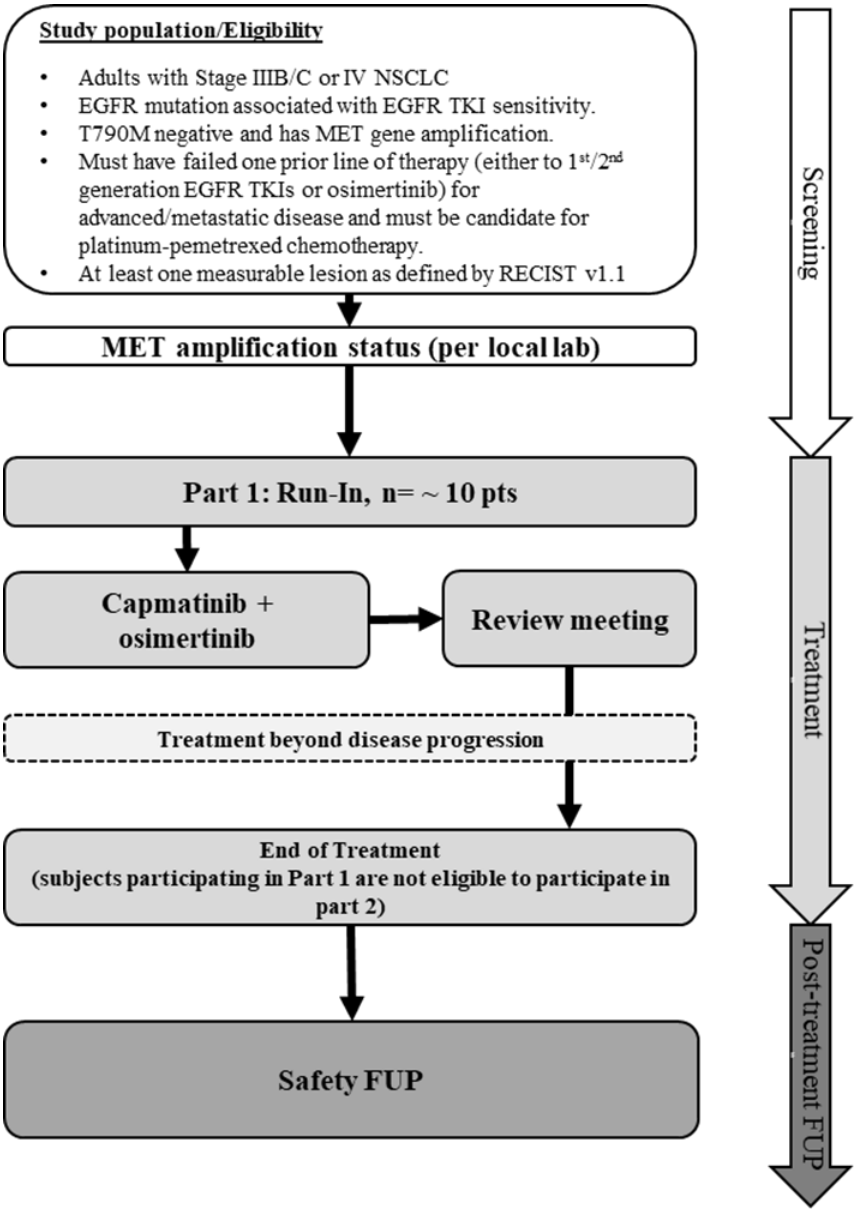
Run-in part:

Approximately 10 participants will be enrolled and treated with dose level 1 (DL1) of 400 mg b.i.d. of capmatinib in combination with 80 mg q.d. of osimertinib, in order to have at least 6 evaluable participants during the dose limiting toxicity (DLT) period (DLT period defined as the first cycle - 1 cycle = 21 days).

A dose level review meeting to evaluate the safety and tolerability of the DL1 will take place after the sixth evaluable participant has been treated for at least 21 days. If DL1 is tolerated, capmatinib 400 mg b.i.d. in combination with osimertinib 80 mg q.d will be the recommended dose for the randomized part.

If DL1 is not tolerated, a second cohort of approximately 10 participants may be added to have at least 6 evaluable participants. This second cohort will be treated at a lower dose level (DL-1) of 400 mg b.i.d. capmatinib in combination with 40 mg q.d. osimertinib. The same rule utilized for the evaluation of DL1 will be utilized to evaluate DL-1. A dose level review team meeting will take place after the sixth evaluable participant of that second cohort has been treated for at least 21 days. If DL-1 is tolerated, capmatinib 400 mg b.i.d. in combination with osimertinib 40 mg q.d will be the recommended dose for the randomized part. If DL-1 is not tolerated, the randomized part will not open.

Figure 1-1 Part 1: Run-in Part



Participants participating in the run-in part are not eligible to participate in the randomized part.

Randomized Part:

The randomized part of the study will not be opened.

1.2 Study objectives, endpoints and estimands

The following Table 1-1 summarizes the original objectives and related enpoints of the study that align with the protocol version 01. To reflect the decision on early termination of the study and given that the randomized part will not be opened, all objectives and endpoints for the randomized part are no longer applicable, only the analyses corresponding to the primary and the secondary endpoints for the run-in part in Table 1-1 will be performed.

Table 1-1 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• Run-in part	• Run-in part
- To confirm the recommended dose of capmatinib in combination with osimertinib	- Incidence of Dose Limiting Toxicities (DLT) during the first 21 days (3 weeks) of treatment for each dose level associated with administration of capmatinib in combination with osimertinib
• Randomized part	• Randomized part
- To compare the progression free survival (PFS) of capmatinib in combination with osimertinib as compared to platinum-pemetrexed	- Progression free survival (PFS) per Blinded Independent Review Committee (BIRC) according to RECIST 1.1.
Key secondary objective(s)	**Endpoint(s) for key secondary objective(s)**
• Randomized part	• Randomized part
- To compare the overall response rate (ORR) of capmatinib in combination with osimertinib as compared to platinum-pemetrexed	- ORR calculated per RECIST 1.1 by BIRC.
- To compare the overall intracranial response rate (OIRR) of capmatinib in combination with osimertinib as compared to platinum-pemetrexed in participants with Central Nervous System (CNS) lesions	- OIRR by BIRC as per RANO-BM criteria.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Run-in part	• Run-in part
- To characterize the safety and tolerability of capmatinib in combination with osimertinib	- **Safety:** Incidence, type, and severity of adverse events per Common Terminology Criteria for Adverse Events (CTCAE) version 5.00 including changes in laboratory values, vital signs, liver assessments and cardiac assessments; **Tolerability:** dose interruptions, reductions, dose intensity, and duration of exposure for all drug components
- To characterize the pharmacokinetics of capmatinib, osimertinib, and osimertinib's active metabolites (AZ5104 and AZ7550) in combination setting	- Plasma PK concentrations and derived PK parameters

Objective(s)	Endpoint(s)
- To assess the tumor response of capmatinib in combination with osimertinib	- All calculated per RECIST 1.1 by investigator: Overall response rate (ORR), Duration of response (DOR), Time to response (TTR), Disease control rate (DCR), Progression free survival (PFS)
• Randomized part	• Randomized part
- To assess the anti-tumor activities of capmatinib in combination with osimertinib as compared to platinum-pemetrexed	- All calculated by BIRC per RECIST 1.1: Duration of response (DOR), Time to response (TTR), Disease control rate (DCR)
- To assess PFS2 (PFS after next-line of treatment)	- PFS2 based on local investigator assessment.
- To evaluate the association between MET amplification status as measured in ctDNA at baseline with PFS and ORR upon treatment with capmatinib in combination with osimertinib	- PFS and ORR by BIRC using RECIST 1.1 criteria for participant with MET amplification as measured in ctDNA at baseline
- To characterize the pharmacokinetics of capmatinib, osimertinib, and osimertinib's active metabolites (AZ5104 and AZ7550) in combination setting	- Plasma PK concentrations
- To evaluate overall survival (OS) in participants treated with capmatinib in combination with osimertinib as compared to platinum-pemetrexed	- Overall Survival
- To evaluate the safety profile of capmatinib in combination with osimertinib as compared to platinum-pemetrexed	- Incidence of adverse events and serious adverse events, change in vital signs, laboratory results and ECG
- To assess the effect of capmatinib in combination with osimertinib as compared to platinum-pemetrexed on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL)	- Change from baseline in European Organization for Research and Treatment of Cancer (EORTC) QLQ-LC13, QLQ-C30, EuroQoL-5 Dimension-5 Level/EQ-5D-5L and NCCN Fact Brain Symptom index questionnaires and time to symptom deterioration for EORTC QLQ-C30, QLQ-LC13 and NCCN FBrSI
- To assess intracranial anti-tumor activity of capmatinib in combination with osimertinib as compared to platinum-pemetrexed in participants with Central Nervous System (CNS) lesions at baseline by BIRC	- Duration of intracranial response (DOIR), time to intracranial response (TTIR), intracranial disease control rate (IDCR) by BIRC as per RANO-BM criteria
[redacted]	

Objective(s)	Endpoint(s)
[redacted]	

2 Statistical methods

The final close-out CSR analysis will be performed by Novartis. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings.

2.1 Data analysis general information

Data from all participants who signed the main informed consent for this study will be used in the analysis. Data collected after participants' withdrawal of informed consent for further participation in the study will not be reported (except for death date, if it is obtained from public records).

Part 1 - Run-in part

The analysis cut-off 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 participants have discontinued study treatment and completed the safety follow-up and approximately 80% of the participants have died, withdrawn consent or are lost to follow-up.
- Another clinical study becomes available that can continue to provide capmatinib and osimertinib combination in this subject population, and all subjects ongoing are eligible to be transferred to that clinical study.

Part 2 - Randomized part

The randomized part of the study will not be opened.

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 participants enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment arm; a missing category will be included as applicable. Percentages will be calculated using the number of participants 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 arm.

2.1.1 General definitions

Unless otherwise specified, definitions below apply for each study part. A participant included in the safety run-in will not enter in the randomized part. Platinum – pemetrexed based doublet chemotherapy is only applicable to the randomized part of the study.

2.1.1.1 Study drug and study treatment

Study drug will refer to capmatinib (INC280) and osimertinib and the control drugs (pemetrexed and cisplatin/carboplatin). Whereas ***study treatment*** will refer to capmatinib in combination with osimertinib or the control treatment (platinum – pemetrexed based doublet chemotherapy).

2.1.1.2 Date of first administration of study drug

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

2.1.1.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug is administered and recorded on the Study Treatment eCRF. The date of last administration of study drug will also be referred as end of study drug.

2.1.1.4 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment (capmatinib/osimertinib or pemetrexed/cisplatin or carboplatin) was administered as per the Study Treatment eCRF.

For example: if 1st dose of capmatinib is administered on 05-Jan-2015, and 1st dose of osimertinib is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015.

2.1.1.5 Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment (capmatinib/osimertinib or pemetrexed/cisplatin or carboplatin) was administered as per the Study Treatment eCRF.

For example: if the last capmatinib dose is administered on 15-Apr-2014, and the last dose of a osimertinib is administered on 17-Apr-2014, then the date of last administration of study treatment is on 17-Apr-2014.

2.1.1.6 Last exposure to study treatment

The date of last exposure to study treatment is derived as the latest date of the last date of exposure to study drug. The last date of exposure to study drug is defined as follows:

- For Capmatinib/Osimertinib: The date of last exposure will be the same as the date of last administration of study drug because of the continuous daily dosing.

'Date of last administration of study drug' is defined in Section 2.1.1.3.

If the derived last date of exposure to study drug/study treatment goes beyond the data cutoff date, it should be truncated to the date of data cutoff.

2.1.1.7 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.

In the Safety run-in part, the reference date for all assessments (safety, efficacy, PK, etc) is the start of study treatment.

'Death' (date of death) will contribute to both efficacy (PFS) and safety analyses. For efficacy and safety, the study will be calculated relative to 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.

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.

2.1.1.8 Baseline

In the Safety run-in part, for safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as "baseline" assessment for both efficacy and safety.

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

2.1.1.9 On-treatment assessment/event and observation periods

For safety reporting (including adverse events), the overall observation period will be divided into three mutually exclusive segments:

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

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

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.

2.1.1.10 Windows for multiple assessments

In order to summarize data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If there are multiple assessments on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

2.2 Analysis sets

Full analysis set

For the safety run-in part, the Full Analysis Set (FAS) comprises all participants that received any component of the study drug.

Safety set

The Safety Set includes all participants who received at least one dose of study treatment (i.e. at least one dose of any component of the study treatment). Participants will be analyzed according to the study treatment actually received, i.e. either capmatinib in combination with osimertinib. FAS and safety set are the same in the run-in part of this study.

Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PAS) includes all participants who provided at least one evaluable PK concentration. For a concentration to be evaluable, participants are required to:

- Have received at least one dose of capmatinib + osimertinib
- For steady state trough samples (pre-dose samples) on or after Cycle 2 Day 1 (C2D1), have taken the consistent dose of capmatinib + osimertinib for at least 5 consecutive days prior to sampling except for Cycle 1 Day 1 (C1D1)
- A PK sample is considered as non-evaluable if it is collected after a participant has vomited within 4 hours post-dose.

Dose-Determining Set (DDS)

The Dose-Determining Set (DDS) includes all participants from the FAS (safety run in parts) who met the minimum exposure criterion and had sufficient safety evaluations, or experienced a dose limiting toxicity (DLT) during cycle 1 (the first 21 days of dosing).

A participant has met the minimum exposure criterion if the participant takes during the first 21 days of dosing at least 75% of the planned doses for each of the combination drugs (i.e. ≥ 16 out of 21 daily doses for capmatinib and ≥ 16 out of 21 daily doses for osimertinib) and at least 50% of the planned combination doses of the two drugs administered together (i.e. ≥ 11 out 21 daily doses).

Participants who do not experience a DLT during cycle 1 (the first 21 days of dosing) are considered to have sufficient safety evaluations if they have been observed for ≥ 21 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.

2.2.1 Subgroup of interest

In **Safety run-in part**, no subgroup analysis will be performed.

2.3 Participant disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all participant disposition and baseline and demographic summaries and listings.

No inferential statistics will be provided.

2.3.1 Participant disposition

The FAS will be used for the participant disposition summary tables and listings.

The number (%) of treated participants will be presented for the Safety Run-in part. The number (%) of participants who are still on treatment, who discontinued treatment, and the primary reason for study treatment discontinuation will be presented.

Screening phase disposition

Screen failures recorded in the screening phase disposition will comprise participants who have been enrolled, i.e. signed the molecular pre-screening ICF, and were (pre-)screened but were not randomized. These participants are not treated with study treatment. Frequency counts and percentages will be tabulated for all enrolled participants as follows:

- Number (%) of participants who completed the screening phase;
- Number (%) of participants who discontinued during the screening phase (participants did not continue into the next phase of the trial);
- Reasons for screening phase discontinuation.

All screen failure participants with reasons for screen failure will be listed. The study allows re-screening of screen failure participants and both the original participant number entered on the re-screen eCRF and the new participant number assigned at re-screening will be used to displayed in the listing.

2.3.2 Demographics and other baseline characteristics

Basic demographic and background data

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively (see Section 2.1).

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will be based on data collected on the eCRF including: primary site of cancer, tumor histology/cytology (predominanat and additional), histological grade, time (in months) since initial diagnosis of

primary site, stage at initial diagnosis and stage at study entry, time (in months) from initial diagnosis to first recurrence/progression, time (in months) since most recent relapse/progression, number and type of metastatic sites, types of lesions (target and non-target lesions) at baseline, number of target lesions at baseline, and disease burden at baseline for target lesion. Metastatic sites will be based on diagnosis eCRF, lesion information will be based on the RECIST eCRF.

Medical history

Relevant medical histories and current medical conditions at baseline will be summarized and listed. The summaries will be presented by primary system organ class (SOC) and 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.

Protocol Deviations

Frequency counts and percentages of participants in the FAS with any important protocol deviations (eligibility, withdrawal, concomitant medication, study treatment, other) will be tabulated by the deviation category. All protocol deviations will be listed.

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

The safety set will be used for all medication data summaries and listings unless otherwise specified.

2.4.1 Study treatment / compliance

The exposure related analyses will be presented by dose regimen for the safety run-in part.

Duration of exposure to study treatment, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized for the study drug. In addition, a categorical summary of RDI will be presented in the respective summaries. The duration of exposure will be categorized into time intervals (<6, ≥ 6–<12, ≥ 12–<18, ≥ 18– <24, ≥ 24–<48, ≥ 48–<72 etc); frequency counts and percentages will be presented for the number (%) of participants in each interval. The number (%) of participants who have dose reductions or interruptions, and the reasons, will be summarized.

Participant level listings of all doses administered on treatment along with dose change reasons will be produced.

Duration of exposure to study drug

Duration of exposure is considered by taking into account the dosing regimen.

- Duration of exposure to study drug (days) = [(last date of exposure to study drug) – (date of first administration of study drug) + 1].

Duration of exposure to study treatment

The duration of exposure to study treatment is defined considering the duration of exposure of each study treatment as:

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

The duration of exposure includes the periods of temporary interruption except for the last one, a dose interruption occurring after the last date of exposure to study treatment won't be considered.

Duration of exposure to study drug/treatment will be categorized into time intervals in weeks. In addition summary statistics will be displayed in weeks.

Cumulative dose

Cumulative dose is defined as the total dose given during the study drug exposure. The cumulative dose is calculated using the information from the study treatment eCRF page and is expressed in mg for all study drugs.

For the combination arm, the actual cummulative dose is the sum of "dose administered" during exposure to capmatinib and osmertinib respectively and is expressed in mg.

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

Dose intensity

Dose intensity (DI) for participants with non-zero duration of exposure is defined as follows:

- For Capmatinib and Osimertinib:

  DI (mg/week) = Actual Cumulative dose (mg) / Duration of exposure to study drug (week).

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

Planned dose intensity

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to participants as per protocol in the same dose unit and unit of time as that of the dose intensity and is defined as follows:

- For Capmatinib and Osimertinib:

  PDI (mg/week) = planned dose as per protocol

Relative dose intensity

Relative dose intensity (RDI) is defined as follows:

- For Capmatinib and Osimertinib:

  RDI (%) = 100 × [DI (mg/week) / PDI (mg/week)].

Dose reductions, interruptions or permanent discontinuations

The number of participants who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized.

Section 5.1 provides further details on the definition of dose changes and interruptions.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of participants who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized.

Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, hormonal therapy etc.), setting (e.g. adjuvant, palliative etc.), number of prior regimens of anticancer medications, setting at last medication (based on the last end date of all prior regimen components). 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.

For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized. For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

The above analyses will be performed using the FAS.

Concomitant antineoplastic radiotherapies

For concomitant radiotherapy, the location, setting, method and lesion subcategory will be summarized based on the FAS. The concomitant radiotherapies will also be listed.

Concomitant therapy

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments and blood transfusions), surgeries or procedures (including physical therapy) administered in the study and are recorded on the eCRFs for Concomitant Medications and Prior or Concomitant non-drug therapies/procedures, respectively.

Concomitant medications will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. Surgeries or procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. All summaries will be tabulated using frequency counts and percentages.

Concomitant therapies will be summarized by lowest ATC class and preferred term. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include: 1) medications starting on or after the start of study treatment but starting no later than 30 days after last dose of study treatment (in the on-treatment period as defined in Section 2.1.1.9) and 2) medications starting prior to the start of study treatment but continuing after the start of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting more than 30 days after the last date of study treatment will be flagged in the listings. The safety set will be used for all concomitant medication tables and listings.

Antineoplastic therapy after discontinuation of study treatment

The FAS will be used for all listings and summaries of antineoplastic therapies initiated after discontinuation of study treatment. All summaries will be tabulated using frequency counts and percentages by cohort.

Antineoplastic medications initiated after discontinuation of study treatment will be summarized and listed by lowest Anatomical Therapeutic Chemical (ATC) class and preferred term.

Antineoplastic radiotherapy since discontinuation of study treatment will be summarized and listed.

Antineoplastic surgery since discontinuation of study treatment will be summarized and listed by SOC and preferred term.

2.5 Analysis supporting primary objective(s)

The primary objective is to confirm the recommended dose of capmatinib in combination with osimertinib. The analysis will be performed on the FAS.

2.5.1 Primary endpoint(s)

The primary endpoint for the safety run-in part is incidence of Dose Limiting Toxicities (DLT) during Cycle 1 of treatment for each dose level associated with administration of capmatinib in combination with osimertinib.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary endpoint for the safety run-in phase is the incidence of DLT during cycle 1. The dose recommendation decision will be based on the following criteria:

- At least six evaluable participants treated at this dose and regimen.
- No more than two DLT have been observed out of six evaluable participants.
- It is the dose recommended for participants after review of all clinical data by Novartis and Investigators in a dose level review team meeting.

If one of the conditions specified above is not satisfied, dose confirmation cannot be declared and a second cohort may be treated at the lower dose level with capmatinib (400 mg b.i.d.) and

osimertinib (40 mg q.d.). The same criteria are applied for this new dose and regimen. If dose confirmation cannot be declared on this lower dose, the randomized part cannot start and the study will end.

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

2.5.3 Handling of missing values not related to intercurrent event

Participants who are ineligible for the DDS will be excluded from the primary analysis of DLT although their data will be used for all remaining analyses. Other missing data will simply be noted as missing on appropriate tables/listings.

2.6 Analysis supporting secondary objectives

The secondary efficacy objective for the safety run-in part is to assess the tumor response of capmatinib in combination with osimertinib

2.6.1 Secondary endpoint(s)

For the run-in part, the secondary efficacy endpoints: ORR, DOR, TTR, DCR and PFS by investigator assessment per RECIST 1.1 will be analyzed.

2.6.1.1 Key secondary endpoints

Not applicable

2.6.1.2 Other secondary efficacy endpoints

2.6.1.2.1 Overall response rate (ORR)

ORR will be assessed in the safety run-in part based on investigator assessment.

ORR is defined as the proportion of participants with confirmed best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1.

The BOR will be determined from response assessments undertaken while on treatment. In addition, only tumor assessments performed before the start of any further anti-neoplastic therapies will be considered in the assessment of BOR. Localized palliative radiotherapy for pre-existing, painful bone and/or liver metastases is permitted when not delivered to a target lesion.

BOR for each participant is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD assessment (or better) >5 weeks after the start of study treatment (and not qualifying for CR or PR).

- PD = progression ≤ 13 weeks after the start of study treatment (and not qualifying for CR, PR or SD)
- NE = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 5 weeks or early progression within the first 13 weeks)

Complete and partial responses must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Participants with 'NE' BOR will be summarized by reason for having NE status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall lesion response NE
- New anti-neoplastic therapy started before first post-baseline assessment
- SD too early
- PD too late

Note 1: A SD is considered as "SD too early"' if the SD is documented within the first 5 weeks after the start of study treatment.

Note 2: A PD is considered as "PD too late" if the first documentation of PD is recorded more than 13 weeks after the start of study treatment with no qualifying CR, PR or SD in between.

Note 3: Special (and rare) cases where BOR is "NE" due to both too early SD and too late PD will be classified as "SD too early".

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

2.6.1.2.2 Duration of response (DOR)

DOR will be assessed in the safety run-in part based on investigator assessment.

DOR only applies to participants whose BOR is CR or PR according to RECIST 1.1 based on tumor response data. DOR is defined as the time from the date of first documented response (CR or PR) to the first documented progression per RECIST 1.1 or death due to any cause. If a participant has not had an event, DOR is censored at the date of last adequate tumor assessment using the censoring rules described in Table 2-1. Participants who never achieved a BOR of CR or PR will be excluded from the analysis. The distribution function of DOR will be estimated using the Kaplan-Meier method. DOR will be analyzed based on the data from the FAS. Median DOR, with corresponding 95% CI, and 25^{th} and 75^{th} percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented.

2.6.1.2.3 Time to response (TTR)

TTR will be assessed in the safety run-in part based on investigator assessment.

TTR is defined as the time from the start of study treatment 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), according to RECIST 1.1. Participants without a confirmed PR or CR will be censored at

- the maximum follow-up time (i.e. FPFV − LPLV) for participants with a PFS event (i.e. disease progression or death due to any cause), or
- at the date of the last adequate tumor assessment date for participants without a PFS event

The distribution function of TTR will be estimated using the Kaplan-Meier method based on data from the FAS. Median TTR, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for TTR proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

2.6.1.2.4 Disease control rate (DCR)

DCR will be assessed in the safety run-in part based on investigator.

DCR is defined as the proportion of participants with a BOR of confirmed CR, PR and stable disease (SD) according to RECIST 1.1.

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

2.6.1.2.5 Progression-free survival (PFS)

PFS will be assessed in the safety run-in part based on investigator.

PFS is defined as the time from the start of study treatment to the first documented progression or death due to any cause per RECIST 1.1. PFS will be censored at the date of the last adequate tumor assessment performed on or before the cut-off date, if no PFS event (progression or death) is observed prior to the analysis cut-off date. Clinical deterioration will not be considered as documented disease progression. PFS events will be included in the analysis if they occur after one missing assessment.

Radiological progression or death observed after 2 or more missing tumor assessments will not be included in the derivation of the time to event for PFS, and the observation will be censored at the time of the last adequate tumor assessment prior to the first missing assessment.

Participants without a post-baseline tumor assessment (and without death) will be censored at the time of the start of study treatment.

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. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the date of the start of study treatment will be used.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is administered; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a tumor assessment (TA) not performed or tumor assessment with

overall lesion response of "NE". 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.

Refer to Table 2-1 for censoring and event date options and outcomes for PFS and Section 5.6 for details regarding missing adequate tumor assessments.

The distribution function of PFS will be estimated using the Kaplan-Meier method based on data from the FAS. Median PFS, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for TTR proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.

Table 2-1 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of start of study 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	Date of last adequate assessment on or prior to starting new anti-cancer therapy	Censored
Death before first PD assessment	Date of death	Progressed

2.6.2 Sensitivity analyses

No sensitivity analyses are planned for the secondary endpoints.

2.7 Safety analyses

For the safety run-in part, summary tables and listings will be presented by dose regimen using the safety set.

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 deaths including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs). The definition of the pre-treatment, on-treatment, and post-treatment period are given in Section 2.1.1.9.

All data, regardless of observation period, will be listed and assessments collected in the post-treatment period will be flagged in all the listings.

2.7.1 Adverse events (AEs)

AEs will be coded using MedDRA using the latest version available prior to clinical database lock and will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

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

Treatment-emergent adverse events (events that started after the first administration of study treatment or events present prior to start of study treatment but increased in severity after the first administration of study treatment, based on preferred term) will be summarized by number and percentage of participants having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) and maximum grade. A participant with multiple occurrences of an AE will be counted only once in the respective AE category. A participant 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 in the investigational drug arm.

The following AE summaries will be produced:

- AEs regardless of study treatment relationship
- AEs suspected to be study treatment related
- On-treatment deaths, by primary system organ class and preferred term
- All deaths, by primary system organ class and preferred term
- SAEs regardless of study treatment relationship

- SAEs suspected to be study treatment related
- AEs leading to permanent discontinuation of study treatment regardless of study treatment relationship
- AEs leading to permanent discontinuation of study treatment suspected to be study treatment related

Clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov and EudraCT, two tables will be provided by SOC and PT based on the safety set:

- On-treatment AEs which are not SAEs with an incidence greater than 5%
- On-treatment SAEs and SAEs suspected to be related to study treatment

If for the same participant, 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.

2.7.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to capmatinib. 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 groupings are specified in the electronic Case Retrieval Strategy (eCRS). The latest version of the eCRS available at the time of the analysis will be used. For each specified AESI, the number and percentage of participants with at least one event of the AESI occurring during the on-treatment period will be summarized. A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.7.2 Deaths

Separate summaries for on-treatment deaths and all deaths will be produced by treatment arm, system organ class and preferred term. All deaths will be listed, and post-treatment deaths will be flagged. A separate listing of deaths prior to start of treatment will be provided for all screened participants.

2.7.3 Laboratory data

For laboratory data assessments, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments collected in the pre-treatment (for baseline, if applicable) and on-treatment period. All laboratory assessments will be listed and those collected in the post-treatment period will be flagged in the listings.

Grading of laboratory values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values (in SI units) only, clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low, normal, or high based on laboratory normal ranges.

- The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment arm):Worst post-baseline CTC grade (regardless of the baseline status). Each participant 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 (hypo and hyper worst grade will be summarized separately, if applicable)
- For laboratory tests where CTC grades are not defined, shift tables using low, normal, high (as well as low and high combined) classification to compare baseline to the worst on-treatment value.
- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 5.0 grades, if applicable, and the classifications relative to the laboratory normal ranges.

All laboratory data will be listed by participant and visit/time, and if normal ranges are available, abnormalities will be flagged.

Liver function parameters

Liver function parameters of interest are total bilirubin (BILI), ALT, AST and alkaline phosphatase (ALP). The number and percentage of participants with worst post-baseline values as per Novartis Liver Toxicity guideline will be summarized. Because the study protocol inclusion criteria allowed participants to be enrolled with elevated baseline ALT or AST values, these are distinguished in the assessment.

The following summaries will be produced:

- Peak post-baseline values

- ALT >3×ULN
- ALT >5×ULN
- ALT >10×ULN
- ALT >20×ULN
- AST >3×ULN
- AST >5×ULN
- AST >10×ULN
- AST >20×ULN
- 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
- BILI >2×ULN
- BILI >3×ULN

- Combined elevations post-baseline
  - AST and ALT ≤ ULN at baseline
  - (ALT or AST >3×ULN) and BILI >2×ULN
  - (ALT or AST >3×ULN) and BILI >2×ULN and ALP ≥ 2×ULN
  - (ALT or AST >3× ULN) and BILI >2× ULN and ALP <2×ULN
- ALT or AST >ULN at baseline
  - (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN
  - (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN and ALP ≥ 2×ULN
  - (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN and ALP <2×ULN

Combined elevations post-baseline are based on the peak values at any post-baseline time for a participant.

(Elevated AST or ALT) is defined as:

- >3×ULN if ≤ ULN at baseline, or
- (>3×BL or >8×ULN) if >ULN at baseline

Potential Hy's Law events are defined as those participants who, depending on their baseline status, fulfill one of the criteria as defined in the Novartis Hepatotoxoicity Guidelines 2019.

Further medical review has to be conducted to assess potential confounding factors such as liver metastases, liver function at baseline etc.

In addition, a listing of the hepatic laboratory values (TBL, ALT, AST and ALP) will be provided with values x.x times above ULN and CTCAE grades flagged. Peak total bilirubin vs peak ALT values will also be graphically presented (eDISH plot).

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

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

The number and percentage of participants with notable ECG values will be presented by treatment arm based on the categories below.

- QT, QTcF
    - 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 ≤ 60 ms
    - Increase from Baseline of >60 ms
- Heart rate
    - 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 by treatment arm and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.7.4.2 Vital signs

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

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

The number and percentage of participants with notable vital signs values will be presented by treatment arm based on the categories below.

Clinically notable elevated values:

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline
- Body temperature: ≥ 39.1°C
- Weight: increase from baseline of ≥ 10%
- Pulse rate: ≥ 100 bpm with increase from baseline of ≥ 25%

Clinically notable values below the normal values:

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Weight: decrease from baseline of ≥ 10%
- Pulse rate: ≤ 50 bpm with decrease from baseline of ≥ 25%

A listing of all vital sign 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 Pharmacokinetic endpoints

The PAS will be used in all pharmacokinetic data analysis and PK summary statistics.

Capmatinib, osimertinib, AZ5104 and AZ7550 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided pre-dose (trough) concentrations by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (coefficient of variation) (arithmetic and geometric), median, minimum, and maximum. Concentrations below lower limit of quantification (LLOQ) will be treated as zero in summary statistics. LLOQ is defined as 1.0 ng/mL for capmatinib and 0.4 ng/mL for osimertinib, AZ5104 and AZ7550.

For C1D1 and C2D1 in run-in part (intensive PK), pharmacokinetic parameters (e.g. AUC, Cmin, Cmax, Tmax, T1/2) will be calculated by noncompartmental methods and listed by participant. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

2.9 PD and PK/PD analyses

Not applicable

2.10 Patient-reported outcomes

Not applicable

2.11 Biomarkers

Not applicable

2.12 Other Exploratory analyses

Not applicable

2.13 Interim analysis

Not applicable

3 Sample size calculation

3.1.1 Primary endpoint(s)

Run-in part

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

3.1.2 Secondary endpoint(s)

Not applicable.

4 Change to protocol specified analyses

Not applicable

5 Appendix

5.1 Dose interruptions and dose changes

This section provides additional details to those included in Section 2.4.1.

All calculations of dose interruptions and dose changes are based on the dose actually taken by the participant.

5.1.1 Definitions for capmatinib and osimertinib

A **dose interruption** is defined as a 0 mg dose taken on one or more days between two non-zero dosing periods. The last zero dose of study drug followed by permanent discontinuation are not considered as dose interruption.

In the case of multiple dose interruptions, these will be handled as follows.

- If an interruption occurs consecutively for at least two days due to the same reason, then it will be counted only once (example: If the actual dose on days 1–3 is 800 mg and actual dose on days 4–5 is 0 mg and dose interruption on days 4–5 is due to AE, then the total number of dose interruptions is 1).
- If an interruption occurs consecutively for at least two days due to different reasons, then it will be counted for each reason (example: If the actual dose on days 1–3 is 800 mg and actual dose on days 4–5 is 0 mg and dose interruption on day 4 is due to AE and dose interruption on day 5 is due to dosing error, then the total number of dose interruptions is 2).
- 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 (example: if the actual dose on days 1, 3 and 5, is 800 mg and actual dose on days 2 and 4 is 0 mg, and dose interruptions on day 2 and 4 are both due to dosing error, the total number of dose interruptions is 2).

A **dose change** is defined as a change in dosing from one record to the next, however a dose interruption will not be counted as a dose change.

Dose reductions are a subset of dose changes where the total daily dose is lower than the previous non-zero dose or differs from the prescribed dose. Some special scenarios are listed below.

Case 1: If a participant did not receive the protocol planned dose for any reason, then this is a dose reduction (400 mg total daily dose, 800 mg total daily dose).

Participant ID	Start date	End date	Prescribed dose (mg b.i.d.)	Total daily dose (mg)	Reason	Reduction (derived)	Comments
0001	22/03/2017	25/03/2017	400	400	DOSING ERROR	**Y**	1st administration different from protocol planned dose (800 mg)
	26/03/2017	26/05/2017	400	800			

Case 2: If, due to a dosing error, a participant receives a higher than the protocol planned dose and moves down to the planned dose then this is not a dose reduction (total daily dose 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, total daily dose 800 mg, 1000 mg, 400 mg, it is a dose reduction).

Participant ID	Start date	End date	Prescribed dose (mg b.i.d.)	Total daily dose (mg)	Reason	Reduction (derived)	Comments
0002	22/03/2017	21/05/2017	400	800			
	22/05/2017	23/05/2017	0	0	ADVERSE EVENT		

Participant ID	Start date	End date	Prescribed dose (mg b.i.d.)	Total daily dose (mg)	Reason	Reduction (derived)	Comments
	24/05/2017	01/08/2017	300	600	ADVERSE EVENT	Y	
	02/08/2017	05/08/2017	400	800			
	06/08/2017	06/08/2017	400	**1000**	**DOSING ERROR**		
	07/08/2017	12/09/2017	400	**800**		**N**	moves down to the dose administered just before dosing error
0003	22/03/2017	21/05/2017	400	800			
	22/05/2017	23/05/2017	0	0	ADVERSE EVENT		
	24/05/2017	01/08/2017	300	600	ADVERSE EVENT	Y	
	02/08/2017	05/08/2017	400	800			
	06/08/2017	06/08/2017	400	**1000**	**DOSING ERROR**		
	07/08/2017	12/09/2017	400	**600**		**Y**	moves down to a lower dose than administered just before dosing error

Case 3: If due to an interruption, a participant receives half of the dose during 1 day, followed by an interruption (due to the same reason) then this is not a dose reduction (e.g. 800 mg total daily dose from 27-Dec-2016 to 14-Jan-2018, and 400 mg total daily dose on 15-Jan-2018, followed by an interruption 16-Jan-2018 to 22-Jan-2018). After the interruption, the dose reduction will be determined using the dose received on a day without interruption (e.g. total daily dose 600 mg vs 800 mg ignoring 400 mg on 15-Jan, given it is related to the interruption).

Participant ID	Start date	End date	Prescribed dose (mg b.i.d.)	Total daily dose (mg)	Reason	Reduction (derived)	Comments
0004	27/12/2017	14/01/2018	400	800			
	15/01/2018	15/01/2018	400	**400**	**ADVERSE EVENT**	**N**	½ dose for 1 day same reason than interruption Interruption started on 15-Jan
	16/01/2018	22/01/2018	0	0	**ADVERSE EVENT**		
	23/01/2018	07/02/2018	400	600	ADVERSE EVENT	**Y**	Dose reduction from 800 mg to 600 mg [400 mg on 15Jan ignored for reduction determination as part of the interruption]
	08/02/2018	19/02/2018	0	0	ADVERSE EVENT		

Participant ID	Start date	End date	Prescribed dose (mg b.i.d.)	Total daily dose (mg)	Reason	Reduction (derived)	Comments
0005	25/04/2016	22/05/2016	400	800			
	23/05/2016	23/05/2016	400	400	ADVERSE EVENT	N	½ dose for 1 day same reason than interruption Interruption started on 23-May
	24/05/2016	25/05/2016	0	0	ADVERSE EVENT		
	26/05/2016	26/05/2016	400	400	ADVERSE EVENT	Y	Dose reduction from 800 mg to 400 mg [400 mg on 23May ignored for reduction determination as part of the interruption]
	27/05/2016	05/06/2016	400	800			
	06/06/2016	06/06/2016	400	400	DOSING ERROR	Y	
	07/06/2016	01/08/2016	400	800			
	02/08/2016	02/08/2016	400	400	**DOSING ERROR**	**Y**	½ dose for 1 day different reason than interruption
	03/08/2016	07/08/2016	0	0	**ADVERSE EVENT**		

Case 4: If due to a permanent discontinuation, a participant receives half of the dose the last day of treatment then this is not a dose reduction (e.g. 800 mg total daily dose from 30-May-2016 to 03-Oct-2016, and 400 mg total daily dose on 04-Oct-2016). This rule is applied for any dose levels (e.g. 600 mg total daily dose from 15-Dec-2017 to 20-Dec-2017, and 300 mg total daily dose on 04-Oct-2016).

Participant ID	Start date	End date	Prescribed dose (mg b.i.d.)	Total daily dose (mg)	Reason	Permanently discontinuation	Reduction (derived)
0006	30/05/2016	03/10/2016	400	800			
	04/10/2016	04/10/2016	200	400	ADVERSE EVENT	Y	**N**

5.1.2 Definitions for cisplatin, carboplatin and pemetrexed

The options ‘dose change’, ‘dose interrupted’, and ‘dose permanently discontinued’ from the study treatment eCRF page for cisplatin, carboplatin and pemetrexed infusion will be used to determine the dose changes, dose interruptions, and permanent discontinuations, respectively.

5.2 Imputation rules

5.2.1 Study treatment

For Capmatinib and Osimertnib

The following rules should be used for the imputation of the dose end date for the study drug:

Scenario 1

If the dose end date is completely missing and there is no end of treatment (EOT) and no death date, the participant is considered as ongoing.

The participant should be treated as ongoing and the cut-off date should be used as the last dosing date.

Scenario 2

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

Case 1: The 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, then use 31DECYYYY.

Case 3: Only year (YYYY) of the dose end date is available and YYYY = the year of EOT date, then use EOT date.

Case 4: Both year (YYYY) and month (MMM) are available for dose end date and YYYY = the year of EOT date and MMM < the month of EOT date, then use last day of the Month (MMM).

Case 5: Both year (YYYY) and month (MMM) are available for dose end date and YYYY = the year of EOT date and MMM = the month of EOT date, then use EOT date.

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

After imputation, compare the imputed date with start date of treatment.

- If the imputed date is < start date of treatment, then use the treatment start date
- Otherwise, use the imputed date

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

5.2.2 AE, concomitant medication (CM) , 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 If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY 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

Missing element	Rule
Day	If available month and year = month and year of study treatment start date then If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01MONYYYY. 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
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*

*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date)

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

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

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications.

5.2.2.1 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 study treatment start date will be replaced with (study treatment start date − 1).

End date

- Imputed date = min (reference end date , last day of the month), if day is missing
- Imputed date = min (reference end date , 31Dec), if month and day are missing

Reference end date will be the start date of study treatment.

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.

Incomplete date of progression – Prior antineoplastic therapy-medication

A missing day is defaulted to the 1st of the month. However, date of progression should be expected to be after start date of prior antineoplastic therapy.

- Imputed date = max (start date of prior antineoplastic therapy, 1st day of the month), if day is missing

5.2.2.2 Post therapies date imputation

Start date

- Imputed date = max (reference start date, first day of the month), if day is missing
- Imputed date = max (reference start date , 01JAN), if day and month are missing

Reference start date will be the last date of study treatment administration + 1.

End date

No imputation.

5.2.2.3 Other imputations

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

A missing day is defaulted to the 15th of the month and a missing month and day is defaulted to 01Jan.

If because of this imputation the chronology of the events is altered then the imputation should be made to the minimum value up to where the chronology remains unchanged. E.g. if due to imputation the date of most recent recurrence becomes prior to the initial diagnosis date then it should be set to initial diagnosis date.

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, the 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 lesion 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 the previous and the following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Incomplete or missing death date

For cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then impute 15th day of the month and year of death.

If both day and month are missing, then impute 01JUL of the year of death.

5.3 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (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).

5.4 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. 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 (see Appendix 5.7 for the current version). 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 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.

5.5 Statistical models

5.5.1 Analysis supporting primary objective(s)

Not applicable

5.5.2 Analysis supporting secondary objective(s)

Kaplan-Meier estimates

An estimate of the survival function in each treatment arm will be constructed using the Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with the

METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE = LOGLOG.

Median survival for each treatment arm 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).

Confidence interval for response rate

Responses will be summarized in terms of percentage rates with $100(1-\alpha)\%$ confidence interval using an exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table (Clopper and Pearson 1934).

5.6 Determination of missing adequate tumor assessments

As detailed in the Study Protocol Appendix 16.1, the PFS censoring and event date options depend on the presence and the number of missing tumor assessments. For example, an event occurring after two or more missing assessments is censored in the analysis of PFS at the last adequate tumor assessment (LATA) before the event date.

An exact rule to determine whether there is none, one or two missing assessments is therefore needed. This rule will be based on the distance between the last adequate tumor assessment date and the event date. If the distance is larger than threshold D1 or D2 then the analysis will assume one or two missing assessments, respectively. The threshold D1 will be defined as the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. Similarly, the threshold D2 is defined as two times the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments.

- In this study, the protocol defined schedule of assessments is:
- every 6 weeks during the first 18 months (i.e. at weeks 6, 12, 18, ... upto week 72),
- every 12 weeks thereafter (i.e. at weeks 84, 96, 108, 120, etc…) up to the primary PFS analysis

Since there is a change of schedule for tumor assessments after first 18 months, D1 and D2 are defined differently depending on when last available tumor assessment occurs:

- In the first 18 months: each assessment is expected to be performed every 6 weeks at the scheduled time point plus or minus 1 week, i.e. the window is 2 weeks, then any distance larger than D1 = 6 + 2 = 8 weeks means one missing assessment and any distance larger than D2 = (2×6) + 2 = 14 weeks means two missing assessments.
- After the first 18 months: each assessment is expected to be performed every 12 weeks at the scheduled time point plus or minus 1 week, i.e. the window is 2 weeks, then any distance larger than D1 = 12 + 2 = 14 weeks means one missing assessment and any distance larger than D2 = (2×12) + 2 = 26 weeks means two missing assessments.

The above definition of D2 will be used to determine the PFS censoring reason. Possible censoring reasons for PFS are:

1: Ongoing without event

2: Lost to follow-up

3: Withdrew consent

4: Adequate assessment no longer available

6: Event after ≥ 2 missing tumor assessments

7: New anticancer therapy given prior to protocol defined progression

The PFS censoring reason is then derived by the following sequence of rules.

- If the participant is considered to have a PFS event then PFS censoring reason is set to missing.
  - Else, if the participant has had no baseline assessment then PFS censoring reason = 4.
  - Else, if the participant has a PFS event after two or more missing assessments [if (PFS event date ≤ censoring date and (PFS event date − date of last adequate tumor assessment (LATA) ≥ D_2)] then PFS censoring reason = 6.
  - Else, if the participant has no PFS event, and the participant is censored at a date after two or more missing assessments ((censoring date − date of LATA) ≥ D_2) then PFS censoring reason = 4.
  - Else, if the censoring date equals the date of discontinuation due to consent withdrawal then PFS censoring reason = 3.
  - Else, if the censoring date equals the date of discontinuation due to loss to follow-up then PFS censoring reason = 2.
  - Else, if the censoring date equals the analysis cut-off date and the time between LATA and the cut-off date is greater than D_2 days then PFS censoring reason = 4.
  - Else, if the censoring date equals the analysis cut-off date and the time between LATA and the cut-off date is less than or equal to D_2 days then PFS censoring reason = 1
  - Else, if the censoring date equals the date of start of new anticancer therapy then PFS censoring reason = 7

Where censoring date = min (analysis cut-off date, date of discontinuation due to consent withdrawal, date of discontinuation due to loss to follow-up).

5.7 Novartis internal criteria for CTC grading of laboratory parameters (based on CTCAE v5 – Nov 2017)

				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 ↓	10^9/L	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	< 1.0 x 10^9/L
WBC (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9/L	-
Hemoglobin (Anemia)	g/L	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	< 100 - 80 g/L < 6.2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB			Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	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↓	10^9/L	LYM		≥1.5x10^9/L	< 1.5 - 0.8 x 10^9/L	< 0.8 - 0.5 x 10^9/L	< 0.5 - 0.2 x 10^9/L	< 0.2 x 10^9/L
Lymphocytes ↑	10^9/L	LYM			-	> 4 - 20 x 10^9/L	> 20 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 *(60 x ukat/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
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	-
Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol/L** or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10.34-12.92 mmol/L > 400 – 500 mg/dL	>12.92 mmol/L > 500 mg/dL
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
Uric acid (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	Defined by clinical criteria only in CTCAE V5				

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

				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**
Phosphorus (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3.0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	Defined by clinical criteria only in CTCAE V5				
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 (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 (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 (non-fasting) (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	Defined by clinical criteria only in CTCAE V5				
Glucose (fasting) (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = 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	< 129 - 125 mmol/L	< 124 - 120 mmol/L	< 120 mmol/L
Triglyceride ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR↑	1	INR	**0.8 – 1.2**	≤ 1.2	> 1.2- 1.5	> 1.5- 2.5	> 2.5	-
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	-
Fibrinogen ↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

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

(1) 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.
Clinical criteria such as 'asymptomatic' or 'Life-threatening consequences' are not considered for determination of LAB CTC grades. Concomitant usage of therapy is also not considered.
Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, ≥ 1.5 x 109 /L (lymphocytes) and ≥ 2 x 109 /L (neutrophils) are considered as LAB CTC grade 0
The comparison with baseline is not considered for derivation of LAB CTC grades

6 Reference

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

Clopper CJ, Pearson ES (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26(4):404–13.

Collet D (1994) Modelling survival data in medical research. London, Chapman & Hall.

Kalbfleisch JD, Prentice RL (2002) The Statistical Analysis of Failure Time Data. 2nd ed; New York: John Wiley & Sons Inc. (available upon request).

Klein JP, Moeschberger ML (1997) Survival Analysis, Nonparametric Estimation of Basic Quantities for Right-Censored and Left-Truncated Data. New York: John Wiley & Sons Inc. (available upon request).