NOVARTIS

Clinical Development

INC280/capmatinib, EGF816/nazartinib

CINC280X2105C / NCT02335944

A phase Ib/II, multicenter, open-label study of EGF816 in combination with INC280 in adult patients with EGFR mutated non-small cell lung cancer

Statistical Analysis Plan (SAP)
Amendment 6 (final CSR)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
18-Jul-2017	Prior to DB lock	Creation of final version	NA – First version	NA
11-Feb-2018	Prior to interim analysis DB lock	Creation of amendment 1	Addition of subgroup definitions and analysis sets for the interim analysis	2.1.2 Reports: The text was updated to state that 2 different TFL shells documents will be created for the IA and the CSR, resp. 2.2 Analysis sets: A subsection 2.2.1 on specific analysis sets for the interim analysis was added. The PPS was updated to be aligned regarding the definition of evaluable subjects. 'Subject Classification' is now section 2.2.3 and the section 'Subgroups of interest' 2.2.4. Two new subsections on brain metastases and on line of therapy were added. A new paragraph 'Interim analysis efficacy analyses by subgroup' was also inserted. 2.14.2 Phase II part: The paragraph on analysis sets was updated to refer to Section 2.2 and 2.2.1.
			Addition of an overview of efficacy analyses	Chapter 5 Appendix: Section 5.5 was added.
			Update to the AESI	2.8.1.1 Adverse events of special interest / grouping of AEs: The section was updated following the change from CRS to eCRS for both INC280 and EGF816.
			Clarifications in the text	1 Introduction: Reference to the RECIST guideline was added, study document versions were updated. 2.3.1 Basic demographic and background data: 25th and 75th percentiles were added as statistics to summarize continuous data. 2.3.3 Subject disposition: Update to the tabulation for protocol deviations.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				2.5.1.2 Statistical hypothesis, model, and method of analysis – Phase Ib: Updated that the posterior distribution of the model parameters and of DLT rates will be presented for the model at the time of MTD declaration and at the end of the Phase Ib. Added that corresponding graphs will be produced. 2.5.2.2.1 Group 1: A typo in the interval for moderate anti-tumor activity was corrected. 2.5.2.4 Supportive analyses: Clarified that reasons for unknown BOR will be presented for both local and BIRC assessment results. 2.8.1 Adverse events (AEs): Update to table SAE with fatal outcome. 6 References: Update to reference Kunzmann (2016). Corrections of typos.
31-Jul-2018	Prior to DB lock for primary analysis (group 3)	Creation of amendment 2	Addition of subgroup for CNS metastases	2.2.5.2 Subjects with CNS metastases: the definition of CNS metastases was added.
			Study documents' versions	1 Introduction: versions of Study specification document and Case Retrieval Sheets were updated.
			Cut-off date for Group 3 primary analysis	2.1.2 Reports: the primary analysis of Group 3 subjects will be performed for internal decision-making.
			Definition of a FAS and safety subset	2.2.3 Subsets for the primary analysis of Group 3 subjects: FAS – 1L subjects and safety set – 1L subjects were defined.
			Definition of first-line patients in Group 4	2.2.5.3 Line of therapy: a new derivation for first-line status of subjects in Group 4 was added.
				2.3.1 Basic demographic and background data, disease history: grouping of metastatic sites (for in-text table) was added.
			Revised the exclusion of Group 2 from efficacy summaries	2.7.1 Secondary endpoints: removed the sentence excluding Group 2. Despite the low number, Group 2 subjects will be included in tables.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Clarification	Several sections: Minor clarifications.
19-Sep-2018	Prior to DB lock for primary analysis (group 3)	Request from upper management	Amendment 3: Adding a summary of time to first dose modification.	2.4.1, Study treatment / compliance: Derivation rule for interruptions was updated. Analysis of time to first dose modification was added.
			Study document versions.	1 Introduction: version of Study specification document was updated.
12-Sep-2020	Prior to DB lock for final analysis	New version of Novartis Hepatotoxicity Guideline; Covid-19-related protocol deviations.	Amendment 4: Addition of outputs for Covid-19 related PDs.	All sections: Text related to analyses other than for the final CSR were removed. Per program standard 'c-MET' was replaced by 'MET'. The list of abbreviations was updated.
			Modified analysis of liver function parameters.	1 Introduction: Versions of study documents were updated.
			Revised to only present the required analyses and specifications for the final CSR.	A paragraph about the impact of the COVID-19 pandemic was added.
				2.1.4 General definitions: Minor clarification for baseline definition.
				2.2.2 Analyses by subgroup: The specific analyses were deleted to avoid having the same information in several sections. Reference is made to the sections 2.7, 2.8 and 2.11.6.
				2.3 Subject disposition, demographics and other baseline characteristics: paragraphs for baseline data that will not be analyzed and presented again were removed.
				2.3.3 Subject disposition: Analysis of COVID-19 related PDs was added.
				2.4.1 Study treatment / compliance: The summary of individual dose interruptions was removed. The specification for dose interruptions ongoing at the time of the data cut-off was changed (not expected for the final analysis).
				Prior anti-neoplastic therapies will not be reported again and the paragraphs were removed.
				2.5.1 Phase Ib: No analysis of the primary objective for Phase Ib will be done and the details were deleted.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				2.5.2.2 Statistical hypothesis, model, and method of analysis – Phase II Groups 1, 2, and 3: The Bayesian estimation of the ORR will not be done for the Final CSR; the related specifications were deleted. 2.5.2.3 Handling of missing values/censoring/discontinuations – Phase II Groups 1, 2, and 3: Additional specifications of censoring for new anti-cancer therapy were added. 2.7.2 Statistical hypothesis, model, and method of analysis (Censoring pattern of OS): reason for death will not be summarized in the OS table, only the number of deaths and censorings. 2.8.3 Laboratory data: Shift tables for lab parameters will not be prepared for the final CSR. The analysis of liver function parameters was modified to align with the current Novartis Hepatotoxicity Guideline. 2.8.4.1 ECG: Change from baseline in ECG parameters by time point was added. 2.8.4.3 ECOG performance status: Summary of performance status by time point was removed. 2.11.5 Derivation of resistance mechanism subgroups for Phase Ib subjects: The subgroup categories for T790M & MET status crossed were updated to also include the missing and the individual categories. 2.11.6 Biomarker analysis: The biomarker summary by response status (BOR) for MET expression was changed to IHC category (instead of H-score). A summary of PFS by biomarker categories (GCN and IHC) was added. Corresponding graphical displays will be generated for the Phase II treatment groups only (BOR and PFS). 5.1.3 Other imputations: the imputation rules for start dates of post-treatment antineoplastic medications were specified in more detail (Table 5-3). 6 References: Typo correction in reference Collett D (1994).

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
06-Nov-2020	Prior to DB lock for final analysis	Update of the last contact date definition	Amendment 5: Update of the last contact date for OS	Update Table 2-1 Last contact date data sources. Date of assessment collected on the "Survival information" eCRF will be considered for last contact date, this is aligned with eCRF completion guidelines (last known date patient alive is not required if subject is reported to be alive)
25-Nov-2021	Prior to DB lock for interim CSR analysis	Cancellation of final analysis and CSR	The previous SAP (amendment 5) for the final CSR analysis will be retired in CREDI	Whole document
25-Nov-2021	Prior to DB lock for interim CSR analysis	Cancellation of final analysis and CSR	Amendment 5 (replacing the retired amendment 5)	List of abbreviations: abbreviations were updated (removed/added). 1 Introduction: Versions of study documents were updated. A paragraph to explain the canceled final CSR was added. A paragraph to explain the purpose of the current SAP was added. The paragraph on COVID-19 pandemic related protocol deviations was moved and updated. 1.1.2 Phase II part: Final CSR was changed to interim CSR. 2.1.1 Data included in the analysis: The paragraph was updated to include a separate cut-off date for efficacy analyses (to be used as censoring date). 2.1.2 Reports: Final CSR was changed to interim CSR. 2.1.4 General definitions: The paragraph on last contact date was updated. 2.2.2.1 Resistance mechanism to EGFR TKI treatment: Update of the derivation of biomarker subgroup status for Phase II subjects (based on biomarker results instead of IRT data). 2.3.3 Subject disposition: An additional analysis of COVID-19 related protocol deviations was added (per Novartis internal guidance).

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				2.5.1 Phase Ib: Final CSR was changed to interim CSR. 2.5.2.2 Statistical hypothesis, model, and method of analysis – Phase II Groups 1, 2, and 3: Final CSR was changed to interim CSR. 2.7.1 Secondary endpoints: the efficacy cut-off date was added (TTR, PFS, OS). 2.7.3 Handling of missing values/censoring/discontinuations: the efficacy cut-off date was added (PFS, OS). 2.9 Pharmacokinetic endpoints: Final CSR was changed to interim CSR. 2.11.1 Introduction: Final CSR was changed to interim CSR. 2.11.4 General data handling and preprocessing: Updated the scope of Table 2-9 to Phase II. Clarified, that the biomarker test method needs to match the protocol requirements to be considered to derive resistance mechanism subgroups. 2.11.5 Derivation of resistance mechanism subgroups: Removed “for Phase Ib subjects” from the subsection title. Also added Phase II in the text. Presentation of the T790M and MET status subgroups was changed to tabular format. 4 Change to protocol specified analyses: A paragraph header was added for each change. 5.1.1 Investigational drug: Final CSR replaced by interim CSR. 6 References: References were updated. General: Correction of typos.
09-Jun-2022	Prior to final DB lock	Converting the interim CSR to the final CSR	Amendment 6	1 Introduction: The list of study documents was removed. The first paragraph was updated to explain that the interim CSR in preparation will be converted to the final CSR.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				In the paragraph header “Information on the cancelled final CSR analysis in 2020” the “in 2020” was added as clarification. The paragraph “Information on the interim CSR” was changed to ”Information on the final CSR” and the text updated. All sections: Interim CSR was updated to final CSR, where applicable.

Table of contents

List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANP	Antineoplastic
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
BIRC	Blinded Independent Review Committee
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Interval
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dosage Administration Record
DBL	Database Lock
DCR	Disease Control Rate
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DOR	Duration Of Response
FAS	Full Analysis Set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EWOC	Escalation With Overdose Control
FDA	Food and Drug Association
FISH	Fluorescence In Situ Hybridization
GCN	Gene copy number
HGLT	High Level Group Terms
HLT	High Level Terms
HR	Heart Rate
IA	Interim analysis
IHC	Immuno-Histo-Chemistry

IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NGS	Next Generation Sequencing
NMQ	Novartis MedDRA Query
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
OSO	Oncology Standard Outputs
PCR	Polymerase Chain Reaction
PDI	Planned dose intensity
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PS	Performance Status
PT	Preferred Term
QTcF	Corrected QT interval using Fridericia correction
RECIST	Response Evaluation Criteria in Solid Tumors
RDI	Relative dose intensity
RP2D	Recommended Phase 2 Dose
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SMQ	Standard MedDRA Query
SOC	System Organ Class
SSD	Study Specification Document
TA	Tumor assessment
TBL	Total bilirubin
TFLs	Tables, Figures, Listings
TKI	Tyrosine Kinase Inhibitor
TTP	Time To Progression
TTR	Time To Response
ULN	Upper Limit of Normal
UNK	Unknown
WBC	White Blood Cell(s)
WHO	World Health Organization
WHO DRL	WHO Drug Reference Listing

1 Introduction

This statistical analysis plan (SAP) describes the analyses for the final Clinical Study Report (CSR) of study CINC280X2105C, a phase Ib/II, multicenter, open-label study of EGF816 in combination with INC280 in adult patients with EGFR mutated non-small cell lung cancer.

[redacted]

COVID-19 pandemic

In addition to the study protocol deviation (PD) terms, Novartis has defined 6 new protocol deviations related to the COVID-19 pandemic and the corresponding relationship (health status related vs. site lockdown, patient concerns, drug supply issue etc.) in line with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" [Food and Drug Administration 2020] and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" [European Medicines Agency 2021]. The following deviations related to the COVID-19 pandemic will be summarized.

- Missing visits
- Changes in procedures and assessments

- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Subject discontinuation due to COVID-19 situation

A cross-tabulation of COVID-19 related PD vs. relationship will also be produced.

Based on a preliminary assessment, the impact on the efficacy and subjects' safety is minimal and no other analyses are planned.

1.1 Study design

This is a phase Ib/II, multi-center, open-label study in adult subjects with EGFR mutated non-small cell lung cancer starting with a Phase Ib dose escalation part followed by a Phase II part.

There is no randomization process, as all subjects will receive the same study treatment.

1.1.1 Phase Ib part

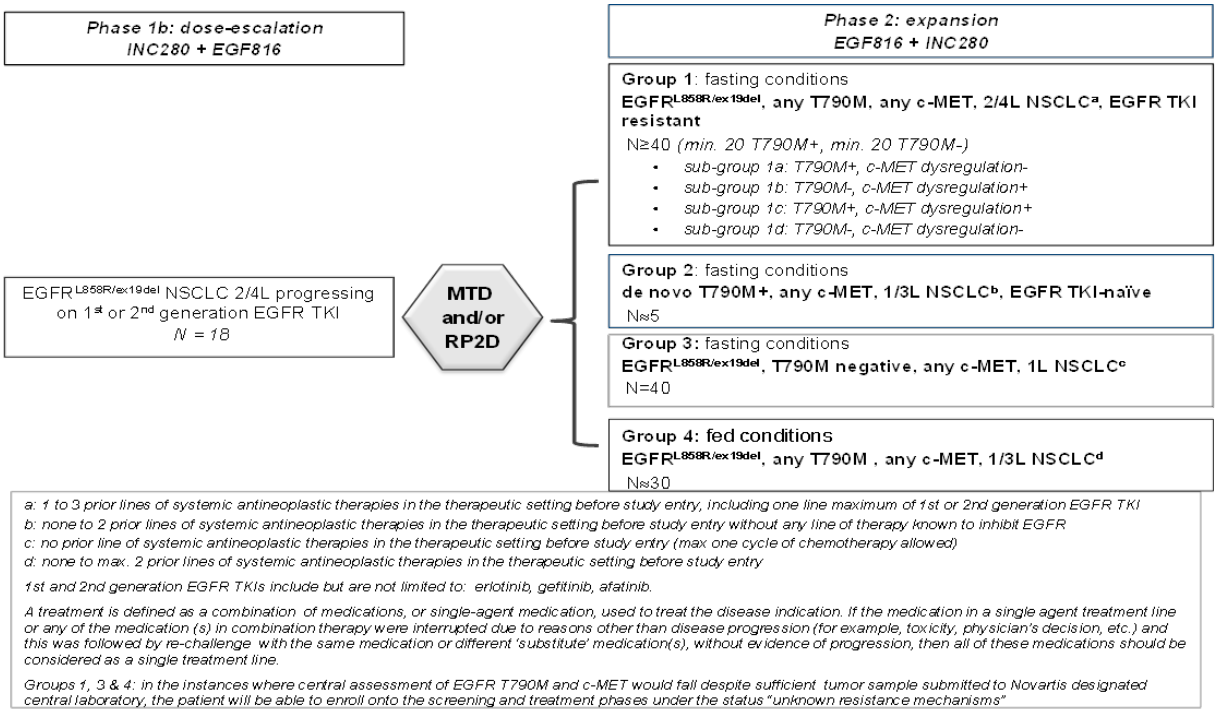
In the Phase Ib part at least 18 subjects who have progressed on previous EGFR TKI treatment (e.g. post erlotinib, gefitinib or afatinib) will be enrolled. An adaptive Bayesian Logistic Regression Model (BLRM) with escalation with overdose control (EWOC) will guide the dose escalation to determine the maximal maximum tolerated dose (MTD) or recommended Phase II dose (RP2D). Before a drug dosage can be declared to be the MTD or RP2D, at least six subjects should have been treated at that dosage.

The incidence of dose limiting toxicities (DLTs) is the primary endpoint for the Phase Ib part.

1.1.2 Phase II part

Once the MTD or RP2D has been declared, approximately 115 additional subjects will be enrolled in the Phase II part, as shown in Figure 1-1, in order to assess the preliminary anti-tumor activity of EGF816 in combination with INC280.

Figure 1-1 Study design



In the Phase II Group 1 (EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant), subjects with a previously documented EGFRmut$^{L858R/ex19del}$ NSCLC, who develop resistance to EGFR TKI treatment (e.g. post erlotinib, gefitinib or afatinib) will be enrolled and assigned according to their acquired resistance mechanism to one of four sub-groups:

- sub-group 1a: EGFRmut$^{L858R/ex19del}$ NSCLC with acquired mutation T790M *(T790M+, MET dysregulation−).*
- sub-group 1b: EGFRmut$^{L858R/ex19del}$ NSCLC with demonstrated MET dysregulation *(T790M−, MET dysregulation+)*.
  MET dysregulation is defined as either
  a. IHC 3+ (defined as ≥ 50% of cells staining with high intensity) and/or
  b. MET gene copy number ≥ 4
- sub-group 1c: EGFRmut$^{L858R/ex19del}$ NSCLC with evidence of both acquired T790M and MET dysregulation *(T790M+, MET dysregulation+)*.
- sub-group 1d: EGFRmut$^{L858R/ex19del}$ NSCLC with MET dysregulation below the levels for sub-group b *(T790M−, MET dysregulation−)*.

At least 40 subjects will be enrolled in the Phase II part Group 1 with a minimum of 20 subjects harboring the T790M mutation among sub-groups 1a and 1c, and a minimum of 20 subjects who do not harbor the T790M mutation among sub-groups 1b and 1d.

The Phase II part Group 2 (EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve) will enroll approximately 5 NSCLC subjects who are EGFR inhibitor treatment (including anti-EGFR monoclonal antibodies) naïve and harbor T790M de novo mutation. The subjects may harbor or may not harbor an EGFR activating mutation (L858R and/or ex19del)

in addition to the EGFR T790M mutation of resistance. The incidence of de novo T790M mutation is rare (~1%). The enrollment in Group 2 will stop once the enrollment in the other groups is completed to allow for completion of recruitment within a reasonable timeframe.

In the Phase II Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic), a minimum of 40 subjects with documented EGFRmut$^{L858R/ex19del}$ NSCLC, who have never received any systemic antineoplastic therapy will be enrolled.

In the Phase II Group 4 (EGFRmut, any T790M, any MET, 1L (treatment naïve) or 2–3L antineoplastic) approximately 30 subjects, with documented EGFRmut NSCLC, who have never received any systemic antineoplastic therapy or have failed a maximum of 2 lines of antineoplastic therapies for advanced disease will be enrolled. Group 4 subjects will take study treatment with food (unrestricted meal type) whilst subjects from all other groups will take the study treatment under fasting conditions. Approximately 10 subjects who are treatment-naïve for the advanced setting should be enrolled in Group 4 in order to collect some safety information on this subject population.

Note for Phase II all groups: subjects who have received no more than 1 cycle of systemic antineoplastic therapy in the advanced setting are allowed.

Treatment-naïve subjects should be enrolled in Group 3 as priority before being enrolled into Group 4. De novo T790M subjects should be enrolled into Group 4 as priority before being enrolled into Group 2.

Overall response rate (ORR), as assessed by local investigators review of tumor response and using RECIST 1.1 criteria, is the primary endpoint in the Phase II of the study.

One interim analysis was conducted for Phase II Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic) when 21 evaluable subjects had completed at least 4 cycles of treatment or discontinued treatment prior to that time.

The primary analysis was conducted based on all subjects' data of the Phase Ib dose escalation part and the Phase II part up to the time when all treated subjects had completed 6 cycles (about 6 months) of treatment. The primary analysis data were summarized in the primary CSR.

[redacted]

1.2 Study objectives and endpoints

Table 1-1 Study protocol objectives and related endpoints

Objective	Endpoint
Primary	
Phase Ib part: To estimate the MTD or RP2D of EGF816 in combination with INC280	Incidence of DLTs
Phase II part: To estimate the preliminary anti-tumor activity of EGF816 in combination with INC280 (Groups 1, 2 and 3)	Overall response rate (ORR) per RECIST v1.1 based on investigator's assessment
To characterize the safety and tolerability of EGF816 in combination with INC280 when taken with food (Group 4)	Safety: Incidence and severity of AEs and SAEs Tolerability: Dose interruptions, reductions and dose intensity

Objective	Endpoint
Secondary	
Phase Ib/II parts: To characterize the safety and tolerability of EGF816 in combination with INC280	Safety: Incidence and severity of AEs and SAEs, including changes in hematology and chemistry values, vital signs and ECGs Tolerability: Dose interruptions, reductions and dose intensity
Phase Ib part: To evaluate the preliminary anti-tumor activity of EGF816 in combination with INC280	ORR, PFS, time to response (TTR), duration of response (DOR) and disease control rate (DCR) based on investigator's assessment and, overall survival (OS)
Phase II part: To evaluate the preliminary anti-tumor activity of EGF816 in combination with INC280	PFS, TTR, DOR, DCR and ORR (Group 4 only) based on investigator's assessment and OS (all Phase II groups)
Phase Ib/II parts: To characterize the PK of EGF816 and INC280 when given in combination under fasted state or with food	Plasma concentration vs time profiles Plasma PK parameters of EGF816 and INC280
[redacted]	[redacted]

The protocol foresees that imaging data will be centrally collected, checked for quality and stored for possible independent review by an imaging CRO designated by Novartis. Meanwhile it was decided to have the independent review performed for subjects treated at the RP2D (Phase Ib and Phase II) and to analyze the results of the central Blinded Independent Review Committee (BIRC) evaluations as supportive for the primary endpoint and secondary efficacy endpoints.

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis personnel.

SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings.

[redacted]

[redacted]

2.1.2 Reports

The outputs will be specified in the Interim CSR TFL shells document.

2.1.3 General analysis conventions

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

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; 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) by treatment group.

Grouping of subjects

Unless otherwise specified, all analyses will be done separately for Phase Ib and Phase II subjects and within each phase by treatment group.

A treatment group is defined by the dose combination of EGF816 and INC280 in the Phase Ib part and by subject group in the Phase II part. Details about the labeling of the treatment groups are provided in the TFL shells document.

For the Phase Ib part, subjects treated with the same initial dose level of EGF816 and INC280 will be pooled into a single treatment group. Both pre and post intra-subject dose escalation data will be listed and summarized together under the initial dose level/treatment group.

For Phase II, summaries and listings will mainly be produced by the 4 groups (Group 1 to Group 4, described in Section 1.1.2). Subjects will be reported according to the group to which they were assigned at baseline based on their mutation status and prior lines of systemic antineoplastic therapies.

Some efficacy and safety outputs will be produced for subgroups. For details regarding the definition of subgroups and the related analyses, please refer to Section 2.2.2, Section 2.5.2.4, and Section 2.7.2.

2.1.4 General definitions

Investigational drug and study treatment

Investigational drug will refer to the individual compound, i.e. INC280 or EGF816, whereas study treatment will refer to the treatment combination INC280 + EGF816.

The term investigational treatment may also be referred to as study treatment, which is used throughout this document.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a nonzero dose of investigational drug is administered and recorded on the 'Dosage Administration Record' (DAR) eCRF. The date of first administration of investigational drug will also be referred to as start of investigational drug or start of study drug.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when a non-zero dose of investigational drug is administered and recorded on the DAR eCRF. The date of last administration of investigational drug will also be referred to as end of investigational drug or last date of exposure to the study drug. (Example: A subject had a permanent discontinuation of the study drug on 06-Jan-2015 after being put on a temporary interruption since 01-Jan-2015. In this case the last date of exposure is 31-Dec-2014).

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered as per the DAR eCRF. (Example: if first dose of INC280 is administered on 05-Jan-2015, and first dose of EGF816 is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015).

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered as per DAR eCRF. (Example: if the last INC280 dose is administered on 15-Apr-2015, and the last dose of EGF816 is administered on 17-May-2015, then the date of last administration of study treatment is 17-May-2015).

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 the 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 the event precedes the reference start date.

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

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative. The displayed study day might be calculated based on an imputed date (see Section 5.1 regarding imputation rules).

Time unit

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

Baseline

For safety and efficacy evaluations, the last available assessment within 28 days on or before the date of start of study treatment is defined as 'baseline' assessment, unless otherwise stated under the related assessment section.

Baseline can be the day before the first administration of study treatment or the same day as first administration of study treatment if a pre-dose assessment/value is available (e.g., ECG, PK samples, samples for biomarkers).

If time is recorded for the first administration of study treatment and for a specific assessment performed on the day of first administration of study treatment, this assessment will be considered as baseline only if the assessment is performed at a time before the first administration of study treatment.

In cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, the following rule will be applied: If values are from central and local laboratories, the value from the central assessment will be considered as baseline. If there are multiple values from the same laboratory (local or central), or collected for ECGs or vital signs, then the last value will be considered as baseline.

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

On-treatment assessment/event and observation periods

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

1. *pre-treatment period*: from day of subject'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 30 + 1 after last administration of study treatment

If a clear assignment to the pre-, on-, or post-treatment period cannot be made, e.g., in case of specific incomplete dates, 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 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.

Windows for multiple assessments

In order to summarize ECG 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 1 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 multiple assessments occur on the same date then the worst case will be used except for ECGs. Three ECGs are targeted to be measured at the protocol-defined (nominal) time-points. If a subject has more than one measurement at a specific time point, the average of all available measurements associated with the nominal time point will be used for the analysis. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Last contact date

The last contact date will be derived for subjects not known to have died at the analysis cut-off [redacted] using the last complete date among the following.

Table 2-1 Last contact date data sources

Source data	Conditions
Last known date patient alive collected on the 'Survival information' eCRF	Subject status is reported to be unknown or lost to follow-up
Date of assessment collected on the 'Survival information' eCRF	Subject status is reported to be alive and missing last known date patient alive
Start/end dates of anti-neoplastic therapies administered after study treatment discontinuation	Non-missing medication or procedure term
Study medication start/end dates from DAR eCRF	Non-missing dose; zero doses are allowed
Date of discontinuation from 'End of Treatment' eCRF and 'End of post-treatment phase' eCRF	None
Start/End dates of AE	Non-missing verbatim AE term
Tumor (RECIST) assessment date	Evaluation is marked as 'done'
Laboratory/PK collection dates	Sample collection marked as 'done'
Vital signs, ECG assessment dates	At least one non-missing parameter value
Performance status dates	Non-missing performance status

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

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

2.2 Analysis sets

Full analysis set

The Full analysis set (FAS) comprises all subjects who have received at least one dose of either INC280 or EGF816. Subjects will be analyzed according to the planned treatment they have been assigned to.

Safety set

The Safety set includes all subjects who received any study treatment (i.e. at least one dose of any component of the study treatment). Subjects will be analyzed according to the study treatment (regimen) they actually received.

The actual treatment received corresponds to:

- the assigned treatment if subjects took at least one dose of that treatment
- the first treatment received if the assigned treatment was never received

Each subject will be classified into and analyzed consistently within one (and only one) combination treatment group.

2.2.1 Subject classification

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

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

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent – INCL01	–
Safety set	No written informed consent – INCL01	–

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 data sets. 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. biomarker, collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.2 Subgroups of interest

The following subgroups will be used in analyses of efficacy.

2.2.2.1 Resistance mechanism to EGFR TKI treatment

Three subgroups will be considered regarding the acquired resistance mechanism to EGFR TKI treatment, based on the acquired T790M mutation status, the MET dysregulation status, and both combined.

For subjects in Phase Ib the subgroup category will be derived from the biomarker results. Details are given in Section 2.11.5.

For subjects in Phase II the subgroup category is collected in the IRT system [redacted]. For the subgroup classification, the biomarker results will be used similar to the Phase Ib case, see Section 2.11.5. The subgroups will be summarized by means of a frequency table (T790M & MET status) and a contingency table (MET dysregulation status vs T790M mutation status) by treatment group. Percentages will be calculated using the number of subjects in the relevant analysis set or subgroup as the denominator.

The subgroups will mainly be used in analyses for the Phase II Group 1. In addition, some analyses for Phase Ib subjects will also be prepared by these subgroups.

Subjects in Phase II Group 3 and Group 4 also have subgroup categories collected in the IRT system. These will only be presented in a listing.

T790M & MET status

- T790M+, MET dysregulation− (Group 1 subgroup a)
- T790M−, MET dysregulation+ (Group 1 subgroup b)
- T790M+, MET dysregulation+ (Group 1 subgroup c1)
- T790M−, MET dysregulation− (Group 1 subgroup c2)
- Other/Unknown (Group 1 subgroup c3)

T790M mutation status

- T790M positive (or short T790M+): subjects with T790M mutation present (Group 1 subgroup a or c1)
- T790M negative (or short T790M−): subjects without acquired mutation T790M (Group 1 subgroup b or c2)
- T790M unknown (or short T790M?): subjects with unknown T790M status (Group 1 subgroup c3)

MET dysregulation status

- MET dysregulated: subjects whose tumor sample analysis shows
  - IHC 3+ (defined as ≥ 50% of cells staining with high intensity) and/or
  - MET gene copy number ≥ 4

  (Group 1 subgroup b or c1)
- MET not dysregulated: subjects without MET dysregulation as defined above (Group 1 subgroup a or c2)

2.2.2.2 Subjects with CNS metastases

The presence or absence of CNS metastases (CNS mets) will be identified from the lesion locations (RECIST eCRF page) at baseline [redacted].

- Category 'CNS mets present': subjects whose lesion locations contain one or more of the following values (case insensitive)

  BRAIN
  BRAIN STEM
  CEREBELLUM
  CEREBRAL CORTEX
  CEREBRUM
  CERVICAL SPINE
  CNS - NOT OTHERWISE SPECIFIED
  CNS: SUPRATENTORIAL
  CNS: INFRATENTORIAL
  CORPUS CALLOSUM
  FRONTAL
  LEPTOMENINGEAL
  LUMBAR SPINE
  OCCIPITAL
  PARIETAL
  PITUITARY
  PONS
  SPINAL CORD
  TEMPORAL
  THALAMUS
  THORACIC SPINE
  WHOLE BRAIN

- Category 'CNS mets absent': will be assigned to all other subjects

For outputs based on the investigator assessment, identification of CNS metastases at baseline will use the data from the investigator review. For outputs based on the BIRC assessment, identification of CNS metastases at baseline will use the data from the BIRC review.

The number of subjects with CNS metastases in target lesions, non-target lesions, and new lesions as well as the responses on target lesions and non-target lesions will be summarized based on investigator and BIRC assessment, respectively.

The CNS metastases subgroups will be used for efficacy analyses of ORR, DOR and PFS.

Note: metastatic sites data collected in the Diagnosis and Extent of Cancer eCRF page will not contribute to the subgroup derivation.

2.2.2.3 Analyses by subgroup

Analyses by subgroups are described in the respective efficacy analysis and biomarker analysis sections. No safety subgroup analyses are planned.

2.3 Subject disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment group and for all subjects and listings will be reported by treatment group to assess baseline comparability. No inferential statistics will be provided. Data will be listed individually by subject.

2.3.1 Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment group. Categorical data (e.g. gender, age groups: <65, ≥ 65–<85, ≥ 85 years, race, ethnicity, ECOG performance status) will be summarized by frequency counts and percentages; the number and percentage of subjects with missing data will be provided. Continuous data (e.g. age, baseline weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum, maximum, 25^{th} and 75^{th} percentile). BMI (kg/m^2) will be calculated as weight [kg] / (height $[m]^2$) using weight at baseline.

Diagnosis and extent of cancer

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

Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on the Diagnosis and extent of cancer eCRF page. [redacted]

2.3.2 Medical history

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

Other

Not all data collected at baseline will be listed again. The corresponding listings were provided in the [Primary CSR].

2.3.3 Subject disposition

The number (%) of subjects in the FAS who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided with percentages based on the total number of FAS subjects:

Study treatment phase

- Number (%) of subjects who are still on-treatment at the time of the data cut-off date for the analysis (based on the 'End of Treatment Disposition' eCRF not completed; for the final analysis the number is expected to be zero and will not be presented)
- Number (%) of subjects who discontinued the study treatment phase (based on the 'End of Treatment Disposition' eCRF)
- Primary reason for study treatment phase discontinuation (based on the discontinuation reason entered in the 'End of Treatment Disposition' eCRF)

Post-treatment follow-up phase for subjects who discontinued the treatment phase

- Number (%) of subjects who did not enter the post-treatment follow-up
- Number (%) of subjects who entered the post-treatment follow-up and are still ongoing at the time of the data cut-off date for the analysis (based on the 'End of Post Treatment Phase Disposition' eCRF; for the final analysis the number is expected to be zero and will not be presented)
- Number (%) of subjects who entered the post-treatment follow-up and have discontinued
- Primary reason for discontinuation from the post-treatment phase

Survival follow-up phase

- Number (%) of subjects who did not enter the survival follow-up (based on the 'End of Treatment Phase' or 'End of Post-treatment follow-up' page)
- Number (%) of subjects who entered the survival follow-up and are ongoing (based on the 'End of Treatment Phase' or 'End of Post-treatment follow-up' page and the 'Survival information' page)
- Number (%) of subjects who entered the survival follow-up and discontinued (based on the 'End of Treatment Phase' or 'End of Post-treatment follow-up' page and the 'Survival information' or 'Death' page)

A listing of study completion by treatment group for Phase Ib and Phase II will be produced separately using the FAS.

Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category and deviation (as specified in the study Data Handling Plan) overall and by treatment group. All protocol deviations will be listed.

An additional table and listing will be provided to summarize and list, respectively, deviations related to the Covid-19 pandemic. A cross-tabulation of COVID-19 related PD vs. relationship will also be prepared.

Analysis sets

The number (%) of subjects in each analysis set (defined in Section 2.2) will be summarized by treatment group using the FAS as denominator. In addition, subjects excluded and reasons for exclusion from each analysis set will be listed.

2.4 Treatments (study treatment, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment group, separately for each component of study treatment. Duration of exposure will also be presented for the study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized by treatment group.

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

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

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drugs:

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

The last date of exposure to study treatment is the latest of the last dates of exposure to any of the investigational drugs (see Section 2.1.4).

Summary of duration of exposure to study treatment will include categorical summaries and continuous summaries (i.e. mean, standard deviation etc.) using the time unit weeks. The following time intervals will be presented: ≤ 4 weeks, 4–≤ 8 weeks, 8–≤ 12 weeks, 12–≤ 16 weeks, 16–≤ 24 weeks, 24–≤ 32 weeks, 32–≤ 52 weeks, 52–≤ 78 weeks and >78 weeks.

Duration of exposure to investigational drugs

Duration of exposure to investigational drug (days) = (last date of exposure to investigational drug) − (date of first administration of investigational drug) + 1.

The last date of investigational drug exposure is defined as the date of last administration of a non-zero dose of the drug (see Section 2.1.4).

For subjects who did not take any drug, the duration of drug exposure is by definition equal to zero.

The exposure duration may include periods of temporary interruption. If a subject is still on treatment at the time of data cut-off, the end date of investigational drug/study treatment will be replaced by the data cut-off date and the above calculations will be applied.

Summary of duration of exposure of investigational drug (INC280, EGF816) will include categorical summaries (based on the same time intervals as for study treatment) and continuous summaries (i.e. mean, standard deviation etc., with time unit day).

Cumulative dose

Cumulative dose of 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 (INC280 and EGF816, respectively).

The *planned cumulative dose* for a study treatment component (INC280 or EGF816) refers to the total planned dose as per the protocol up to the last date of investigational drug administration. The planned cumulative dose will not be summarized or listed. It will be 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 DAR eCRF.

For subjects in the Safety Set who did not take one component of study treatment the cumulative dose for that component is by definition equal to zero.

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

Dose intensity and relative dose intensity

Dose intensity (DI) for subjects with non-zero duration of exposure is defined as follows for each of the study treatment components (INC280, EGF816):

DI (mg/day) = actual cumulative dose (mg) / duration of exposure (days).

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

Planned dose intensity (PDI) is defined as follows:

PDI (mg/day) = planned cumulative dose (mg) / duration of exposure (days).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/day) / PDI (mg/day).

DI and RDI will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components. The summary of RDI includes categorical summaries for RDI expressed as percentage for the following intervals: ≤ 75%, >75–90%, >90–110%, ≥ 110%.

Dose reductions, interruptions or 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 (INC280, EGF816).

'Dose interrupted' and 'Dose permanently discontinued' fields from the DAR eCRF together with the dose taken will be used to derive the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding field 'Reason for dose change/dose interrupted' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

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

Interruption: To derive dose interruptions at the end of the treatment period or around the date of the cut-off, the following rules will be used.

- A dose interruption followed by a permanent discontinuation will be counted as permanent discontinuation, not as interruption.
- A dose interruption which is ongoing at the time of the data cut-off is not expected for the final analysis; such cases will be considered as a permanent discontinuation.

Reduction: 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 dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

2.4.2 Prior, concomitant and post therapies

Anti-neoplastic medications and concomitant medications will be coded using the WHO Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system. Anti-neoplastic surgery as well as concomitant surgical and medical procedures will be coded using MedDRA. Details regarding MedDRA and WHO DRL version will be included in the footnote in the tables/listings.

Prior anti-cancer therapy

The number and percentage of subjects who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery was summarized in the [Primary CSR] and will not be reported.

Post-treatment anti-cancer therapy

Anti-neoplastic medications since discontinuation of study treatment will be summarized by ATC class, preferred term, overall and by treatment group by means of frequency counts and percentages using the FAS. Separate listings will be produced for medications, radiotherapies, and surgeries.

Concomitant medications

Concomitant therapy is 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 includes medications (other than investigational 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 summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be summarized by SOC and preferred term. These summaries will include:

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

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

2.5 Analysis of the primary objective

2.5.1 Phase Ib

The primary objective of the study's Phase Ib part is to estimate the MTD or RP2D of EGF816 in combination with INC280 in $EGFR^{L858R/ex19del}$ NSCLC subjects who have progressed on EGFR TKI treatment (e.g. gefitinib, erlotinib, or afatinib).

The primary objective for the Phase Ib was analyzed in the primary analysis and reported in the [Primary CSR]. No analysis will be done for the final CSR.

2.5.2 Phase II

The primary objective of the Phase II part is to estimate the preliminary anti-tumor activity of EGF816 in combination with INC280 measured by ORR determined by the Investigators' assessment in accordance with RECIST 1.1 in each of the groups 1 to 3. In Group 4 the primary

objective is to characterize the safety and tolerability of EGF816 in combination with INC280 when taken with food.

The primary objective for the Phase II was analyzed in the primary analysis and reported in the [primary CSR]. The analyses described below will be updated including the data collected for subjects ongoing at the cutoff date for the primary analysis.

2.5.2.1 Primary endpoint – Phase II Groups 1, 2, and 3

ORR is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 (see [CSP Appendix 1]). ORR will be calculated based on the FAS using local investigators review of tumor assessment data. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR. Radiotherapy to the bone or central nervous system (CNS), and surgical resection of CNS metastases as well as palliative bone radiotherapy is allowed as per protocol, and will not be considered in determining antineoplastic therapy usage.

The ORR will be estimated by group or sub-group as assigned based on baseline mutation status and prior systemic antineoplastic therapy. The following groups will be considered (see also Section 1.1.2).

- Group 1, EGFRmut, any T790M, any MET, 2/4L antineoplastic, EGFR TKI resistant
- Group 2, EGFRmut, de novo T790M, any MET, 1/3L antineoplastic, EGFR TKI naïve
- Group 3, EGFRmut, T790M negative, any MET, 1L antineoplastic first line

Best overall response

BOR is the best response recorded from the start of the treatment until documented radiological disease progression/recurrence. However, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation.

The study requires that for a partial response (PR) or complete response (CR) changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for the response are first met.

The best overall response for each subject 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 the end of treatment.
- PR = at least two determinations of PR or better at least 4 weeks apart before the end of treatment (and not qualifying for a CR).
- SD = at least one SD assessment (or better) >7 weeks after start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 17 weeks after start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 7 weeks or early progression within the first 17 weeks).

Subjects discontinuing from the study for PD must have it documented by radiologic evaluation. In cases of clinically-evident disease progression, all efforts should be made to perform a radiologic evaluation. Subjects with symptoms of rapidly progressing disease without radiologic evidence will not be classified as progression.

2.5.2.2 Statistical hypothesis, model, and method of analysis – Phase II Groups 1, 2, and 3

The Bayesian model employed for the primary analysis will not be repeated.

For the final CSR frequencies of the BOR categories will be presented and the response rate will be summarized using descriptive measures including 95% confidence intervals (CI) using the exact method [Clopper and Pearson 1934].

Individual lesion measurements and overall response at each assessment will be listed by group and subject.

2.5.2.3 Handling of missing values/censoring/discontinuations – Phase II Groups 1, 2, and 3

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

Censoring for new anti-cancer therapy

For BOR only tumor assessments performed before the start of any new anti-cancer therapy (including medication, radiotherapy and surgery) will be considered.

PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date or before the start of the new anti-cancer therapy date, whichever is earlier.

The protocol allows radiotherapy to the bone or central nervous system (CNS), and surgical resection of CNS metastases as well as palliative bone radiotherapy (that is, these will not lead to censoring).

Derivation of new anti-cancer therapy

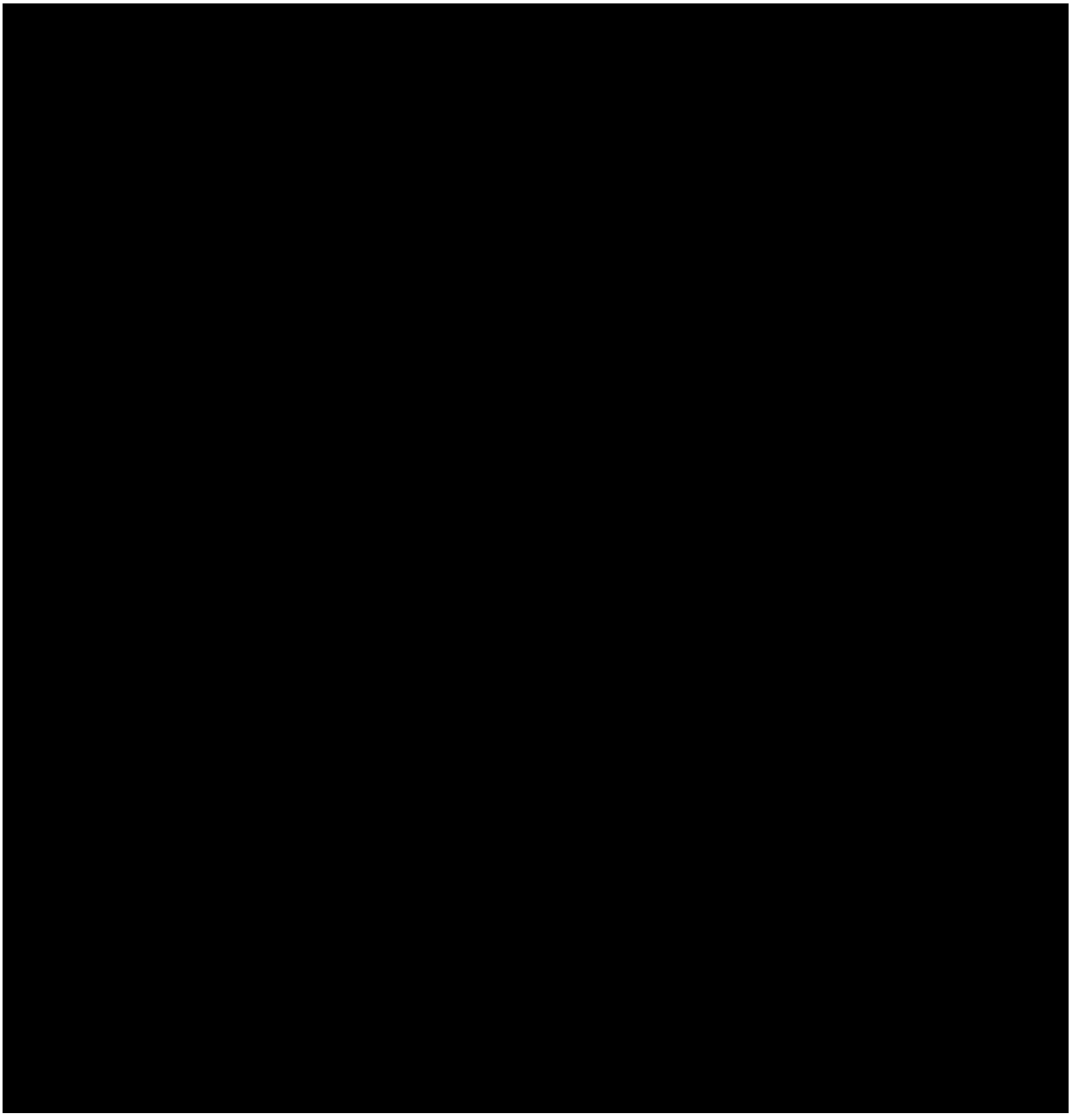
To determine the use of new anti-cancer therapy, data entered in the following CRFs will be considered [redacted]:

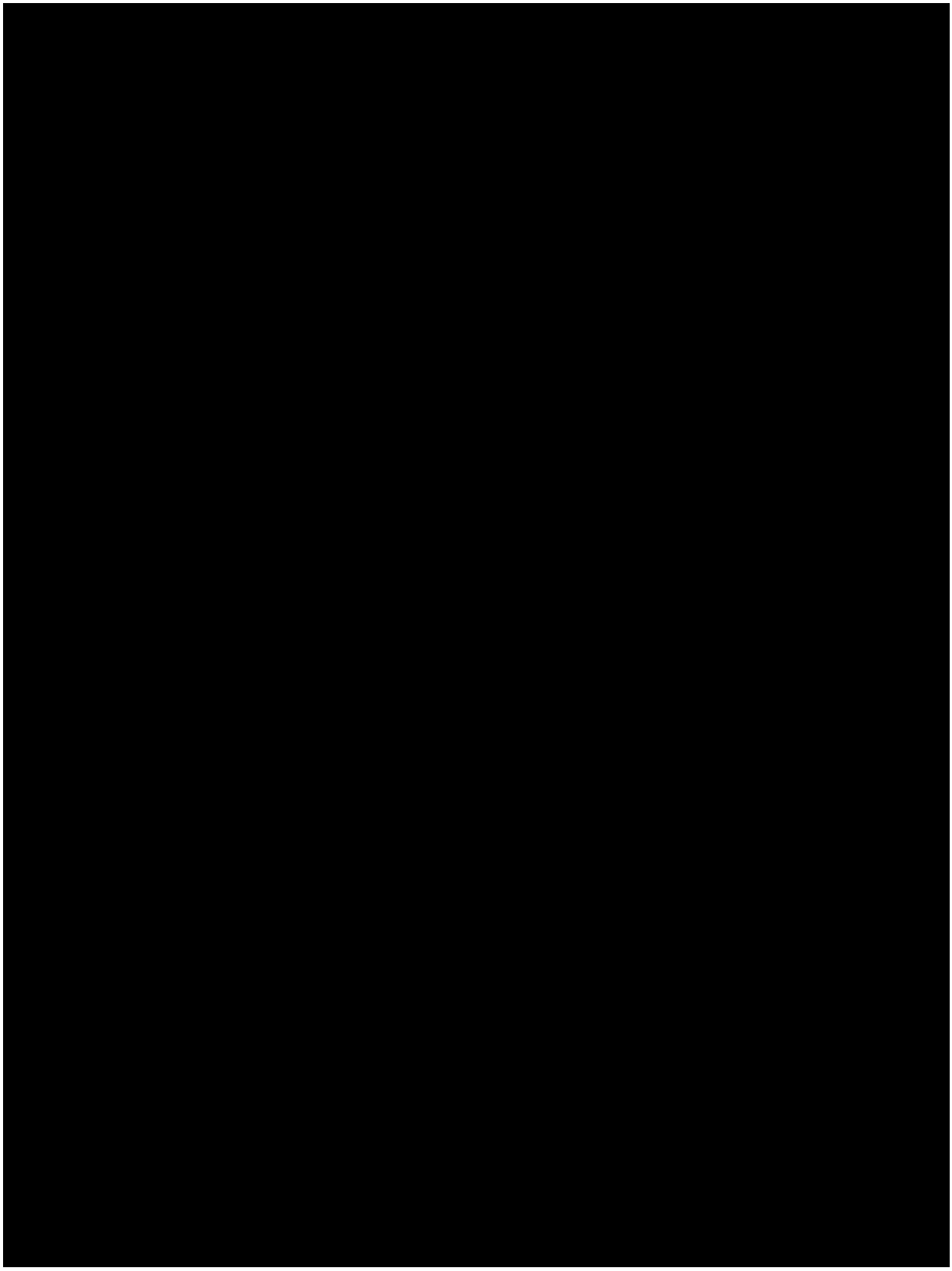
- Antineoplastic Therapy Since Discontinuation of Study Treatment – Medication,
- Antineoplastic Therapy Since Discontinuation of Study Treatment – Radiotherapy,
- Antineoplastic Therapy Since Discontinuation of Study Treatment – Surgery.

In addition certain therapies entered in the CRF Prior and Concomitant Medications (domain CM) will be considered, if they were started after start of study treatment.

Medications in CM will be taken into consideration if they are anti-cancer therapies, as determined from the project-wide list for therapy type (updated with anti-cancer medication yes/no).

Radiotherapies and surgeries in CM will be considered except if the MedDRA preferred term is ‘radiotherapy to brain’ or ‘gamma radiation therapy to brain’ or some synonym of these. Cases where the preferred term is radiotherapy or radiation without giving a location and the indication is ‘brain metastasis’, ‘brain metastases’, or some synonym will also be excluded. Radiation to other locations like for example lung will lead to censoring.





2.5.2.5 Primary endpoint – Phase II Group 4

Frequencies of treatment-emergent AEs will be calculated to characterize the safety and tolerability of the study treatment. The Safety Set will be used for summary tables.

2.5.2.6 Statistical hypothesis, model, and method of analysis – Phase II Group 4

Adverse events will be analyzed as described in the section on safety analysis, Section 2.8.1.

2.5.2.7 Handling of missing values/censoring/discontinuations – Phase II Group 4

Summary tables for AEs will include events collected in the on-treatment period. If dates are incomplete and no clear assignment to pre-, on-, or post-treatment period can be made, then on-treatment will be assumed (see Section 5.1.2).

2.6 Analysis of the key secondary objective

No key secondary objective was defined.

2.7 Analysis of secondary efficacy objectives

The secondary efficacy objective for Phase Ib as well as Phase II is to evaluate the preliminary anti-tumor activity of EGF816 in combination with INC280.

2.7.1 Secondary endpoints

The secondary efficacy endpoints in Phase Ib and Phase II are BOR, ORR (if not already part of the primary analysis), disease control rate (DCR), duration of response (DOR), time to response (TTR), and progression-free survival (PFS). These endpoints are based on investigator assessment in accordance with RECIST 1.1. An additional endpoint is overall survival (OS).

For supportive analyses BOR, ORR, DCR, DOR, TTR, and PFS will also be evaluated based on the BIRC review of tumor data in accordance with RECIST 1.1. For Phase Ib data the independent review will only be performed for subjects from cohorts with the RP2D.

The secondary efficacy endpoints will be analyzed using the FAS.

Overall response rate and best overall response

See definitions in Section 2.5.2.1.

Duration of response

DOR only applies to subjects whose best overall response is CR or PR according to RECIST 1.1 based on local investigators or BIRC review of tumor assessment data. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to any cause. Subjects continuing without progression or death will be censored at the date of their last adequate tumor assessment using the censoring rule described for the PFS analysis.

Disease control rate

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

Time to response

TTR is the time from date of first administration of study treatment to first documented response of CR or PR (which must be confirmed subsequently) using local investigators or BIRC review of tumor assessment data and according to RECIST 1.1. Subjects who did not achieve a confirmed PR or CR will be censored at:

- the maximum follow-up time (i.e. FPFV − LPLV used for the analysis in the respective subject group) for subjects who had a PFS event (i.e. either progressed or died due to any cause); [redacted]
- the last adequate tumor assessment date for all other subjects

Progression-free survival

PFS is defined as the time from the date of first administration of study treatment to the date of the first documented progression or death due to any cause. PFS will be based on local investigators or BIRC review of tumor assessments and using RECIST 1.1 criteria (see [CSP Appendix 1]). PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date [redacted] or before the start of the new anti-cancer therapy date, whichever is earlier. (See Section 2.7.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment, see Section 2.5.2.1 regarding exceptions in determining anti-cancer therapy usage). Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition pages without supporting objective evidence satisfying progression criteria per RECIST 1.1 will not be considered disease progression for PFS derivation. Clinical deterioration will not be considered as a qualifying event for progression.

Overall survival

OS is defined as the time from date of first administration of study treatment to date of death due to any cause. All deaths occurring on or before the efficacy cut-off date will be used in the OS analysis. If a subject is not known to have died at the time of the analysis, the OS time will be censored at the date of last contact.

2.7.2 Statistical hypothesis, model, and method of analysis

ORR, BOR, and DCR

ORR and DCR will be summarized using descriptive statistics (N, %) by treatment group (Phase Ib) or group (Phase II) along with two-sided exact binomial 95% CIs [Clopper and Pearson 1934]. As a supportive analysis ORR and DCR based on the BIRC review of tumor data will also be summarized. Frequencies of the BOR categories will also be presented. Subjects with 'unknown' BOR will be summarized by reason for having unknown status (see Section 2.5.2.4) based on both investigator and BIRC assessment. A concordance analysis of BOR (see Section 2.5.2.4) will be provided for Phase Ib (RP2D) and Phase II groups.

A listing will be presented with overall responses at all assessment timepoints, with percentage change from baseline, difference between NADIR and sum of diameters, and BOR per subject.

Waterfall plots based on both investigator and BIRC assessment will be prepared per treatment group.

Time to event endpoints

TTR, DOR, PFS and OS data will be listed and summarized by treatment group. The distribution of TTR, DOR, PFS, and OS, respectively, will be estimated using the Kaplan-Meier method. The results will be presented graphically. The median, 25th and 75th percentiles along with 95% CI will be presented along with the survival probabilities at 6, 9, 12, 18, and 24 months and their associated 95% CI.

These analyses will be based on both investigator and BIRC assessment.

Listings of TTR and DOR details as well as PFS and OS data by treatment group (Phase Ib) and Phase II group will be provided.

Censoring pattern of PFS

The number of subjects with a PFS event and the number of subjects censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided by treatment group based on the following reasons:

1. Ongoing without event
2. Lost to follow-up
3. Withdrew consent
4. Adequate assessment no longer available
5. Initiation of new cancer therapy prior to progression
6. Event after ≥ 2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate tumor assessment (TA) date and the earliest of the following dates is less than or equal to the interval of 2 missing TAs (see Section 2.7.3 for definition):

1. Analysis cut-off date
2. Start date of further anti-neoplastic therapy
3. Date of consent withdrawal
4. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up

Then the PFS censoring reason will be:

1. ‘Ongoing’
2. ‘New cancer therapy added’
3. ‘Withdrew consent’
4. ‘Lost to follow-up’

If the time interval is larger than the interval of 2 missing TAs with no event observed, then the PFS censoring reason will always default to 'Adequate assessment no longer available'. If the time interval between the last adequate TA date and the PFS event date is larger than the interval of 2 missing TAs then the subject will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

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

Censoring pattern of OS

The pattern of censored data will be examined regarding reasons for censoring ('Alive' or 'Lost to follow-up'). In addition, survival status, reason for censoring and cause of death will be listed.

Subgroup analyses for secondary efficacy endpoints

For the secondary efficacy endpoints the following subgroup analyses will be prepared.

The ORR and DCR summaries based on investigator and BIRC assessment will be analyzed by T790M mutation status and MET dysregulation status for Phase Ib subjects. Overall survival will be analyzed by MET dysregulation status.

2.7.3 Handling of missing values/censoring/discontinuations

ORR

See Section 2.5.2.3.

TTR

Subjects who did not achieve a confirmed PR or CR will be censored as described in Section 2.7.1.

DOR

Subjects continuing without progression or death will be censored at the date of their last adequate tumor assessment using the censoring rule described for the PFS analysis.

PFS

PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the [redacted] analysis cut-off date or before the start of the new anti-cancer therapy date, whichever is earlier.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. 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 start date of 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 anti-cancer therapy was administered (see also Section 2.5.2.3); the event occurred after two or more missing tumor assessments.

The term 'missing adequate tumor assessment' is defined as a TA not performed or TA with overall lesion response of 'UNK'. The rule to determine the 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 2-4 for censoring and event date options and outcomes for PFS.

Table 2-4 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Start date of treatment	Censored
Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Date of last adequate assessment	Censored
New anti-cancer 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

OS

If a subject is not known to have died at the time of the analysis, then OS time will be censored at the date of last known date subject was alive, i.e., last contact date (see Section 2.1.4). If the tick box for 'Lost to follow-up' is ticked on the 'Survival information' eCRF or if the time between the last contact date and the [redacted] analysis cut-off date is longer than the protocol specified interval between the survival follow-up assessments plus 2 weeks, i.e., 15 weeks for this study (3 × 30.4375 + 14 days = 91.3125 + 14 days = 105.3125 days ≈ 15 weeks), subjects OS time will be censored for 'Lost to follow-up'.

2.8 Safety analyses

All safety analyses will be based on the safety set. All listings and tables will be presented by treatment group and will include Phase Ib and Phase II groups. For individual subject data listings in section 16 of the CSR the FAS will be used.

2.8.1 Adverse events (AEs)

Coding and grading of AEs

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. The grading is done according to the Common Terminology Criteria for Adverse Events (CTCAE). See Section 5.2 in the appendix for further details.

AE summaries

AE summaries will include all AEs occurring during the on-treatment period (see Section 2.1.4). 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 treatment, AE outcome etc. AEs with start date outside of the on-treatment period will be flagged in the listings.

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

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the 'All subjects' column combining subjects from Phase Ib and Phase II.

The following adverse event summaries will be produced:

- Overview of adverse events and deaths
- AEs regardless of study treatment relationship (including CTC grade 3/4)
- AEs suspected to be study treatment related (including CTC grade 3/4)
- AEs regardless of study treatment relationship leading to discontinuation of study treatment
- AEs suspected to be study treatment related leading to discontinuation of study treatment
- AEs regardless of study treatment relationship requiring dose adjustment or study treatment interruption
- SAEs regardless of study treatment relationship
- SAEs suspected to be study treatment related
- SAEs with fatal outcome

In addition, tables required for ClinicalTrials.gov and EudraCT will be provided (see Section 2.8.1.2).

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to the compound INC280 and/or EGF816. These groupings are

defined using MedDRA terms, standardized MedDRA queries (SMQs), high level group terms (HGLTs), high level terms (HLTs) and PTs. 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.

The adverse events of special interest to be monitored for INC280 and for EGF816 are specified in the respective electronic Case Retrieval Sheet (eCRS). [redacted]

The most recent version of the eCRS at the time of DBL or data snapshot will be used. The codes of the search terms related to the AESIs will be used to generate outputs. The eCRS version will be included in a footnote of the AESI tables.

For each specified AESI, the number and percentage of subjects with at least one event of the AESI occurring during the on-treatment period will be summarized (in separate tables for INC280 and EGF816).

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

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

[redacted]

2.8.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment deaths) will be produced by treatment group, system organ class and preferred term.

All deaths will be listed, post-treatment deaths will be flagged.

2.8.3 Laboratory data

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. 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 2.1.4).

A summary of the worst post-baseline CTC grade (regardless of the baseline status) will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment group). Each subject will be counted only for the worst grade observed post-baseline.

The following listings will be produced for the laboratory data (including urinalysis):

- Listings of hematology data (primary hematology variables, WBC and differentials, coagulation) and biochemistry data (g, renal) with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities
- Listing of hepatitis B and C monitoring (during the trial)

Liver function parameters

Liver function parameters of interest are total bilirubin (BILI), ALT, AST and alkaline phosphatase (ALP). The number (%) of subjects with worst post-baseline values as per Novartis Liver Toxicity guideline will be summarized. Because the protocol (inclusion criteria) allowed subjects 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 >8×ULN
  - ALT >10×ULN
  - ALT >20×ULN
  - AST >3×ULN
  - AST >5×ULN
  - AST >8×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
    a. (ALT or AST >3×ULN) and BILI >2×ULN
    b. (ALT or AST >3×ULN) and BILI >2×ULN and ALP ≥ 2×ULN
    c. (ALT or AST >3× ULN) and BILI >2× ULN and ALP <2×ULN
  - ALT or AST >ULN at baseline
    a. (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN
    b. (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN and ALP ≥ 2×ULN
    c. (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 subject.

(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 subjects who, depending on their baseline status, fulfill one of the criteria. 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).

2.8.4 Other safety data

2.8.4.1 ECG

Data handling

Triplicate ECGs are required at all assessments. The average of the ECG parameters at an assessment (including baseline) will be used in the analyses.

If a subject has more than one post-baseline measurement at a specific time point, the average of all available measurements associated with the nominal time point will be used.

Data analysis

Standard 12-lead ECGs including PR, QRS, QT, QTcF, and HR 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 by treatment group:

- 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

- HR
  - Increase from baseline >25% and to a value >100 bpm
  - Decrease from baseline >25% and to a value <50 bpm
- PR
  - Increase from baseline >25% and to a value >200 ms
  - New value of >200 ms
- QRS
  - Increase from baseline >25% and to a value >120 ms
  - New values of QRS >120 ms

Change from baseline in ECG parameters by time point will be presented by treatment group.

A listing of all ECG assessments will be produced by treatment group and notable values will be flagged. A separate listing of only the subjects with notable ECG values will also be produced. In the listings, the assessments collected during the post-treatment period will be flagged.

2.8.4.2 Vital signs

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

Data handling

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

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-5 below.

Table 2-5 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	below normal value
Weight (kg)	increase >10% from baseline	decrease >10% from baseline
Systolic blood pressure (mmHg)	≥ 180 with increase from baseline of ≥ 20	≤ 90 with decrease from baseline of ≥ 20
Diastolic blood pressure (mmHg)	≥ 105 with increase from baseline of ≥ 15	≤ 50 with decrease from baseline of ≥ 15

Vital sign (unit)	Clinically notable criteria	
	above normal value	below normal value
Pulse rate (bpm)	≥ 100 with increase from baseline of >25%	≤ 50 with decrease from baseline of >25%
Body temperature (°C)	≥ 39.1	–

The number and percentage of subjects with notable vital sign values (high/low) will be presented by treatment group.

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

2.8.4.3 ECOG performance status

The ECOG PS scale (Table 2-6) will be used to assess physical health of subjects, ranging from 0 (most active) to 5 (least active).

Table 2-6 ECOG performance scale

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

ECOG performance status at baseline will be presented in the demographics listing.

2.9 Pharmacokinetic endpoints

Analyses of pharmacokinetic data were provided in the primary CSR. No analyses will be done for the final CSR.

2.10 Patient-reported outcomes

Not applicable.

2.11 Biomarkers

2.11.1 Introduction

As a project standard, only biomarkers collected in the clinical database will be analyzed. [redacted]

[redacted]

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

[redacted]

The FAS will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on subjects with biomarker data.

[redacted]

2.11.3 List of biomarkers evaluated and the collection time points

The biomarkers evaluated in the study are listed in Table 2-7 and Table 2-8 below. For further details refer to [CSP Section 7.2.4].

Table 2-7 Sample biomarker summary table – Phase Ib part

Biomarker	Time point	Sample	Method
Activating EGFR mutation, L858R or ex19Del	Pre-screening	Tumor	Local: Any method
MET	Pre-screening	Tumor	Local: FISH or IHC, any method
		Tumor (newly obtained formalin-fixed biopsy [preferred] or archival tumor block or slides of a formalin fixed paraffin embedded biopsy)	Central: FISH and/or-IHC
EGFR T790M	Pre-screening	Tumor	Local: Qiagen therascreen (PCR) or Roche Cobas (PCR) (all countries except USA)

Biomarker	Time point	Sample	Method
		Tumor (preferably same specimen as for MET)	Central: PCR
[redacted]			
Cell-free DNA	Screening or C1D1 (pre-dose), C3D1 and every 3rd cycle, EOT	Blood	Central: PCR, NGS and/or other methods

Table 2-8 Sample biomarker summary table – Phase II part

Biomarker	Time point	Sample	Method
Activating EGFR mutation, L858R or ex19Del	Pre-screening	Tumor	Local: Any method
MET	Pre-screening	Tumor (newly obtained formalin-fixed biopsy [preferred] or archival tumor block or slides of a formalin fixed paraffin embedded biopsy)	Central: FISH and/or-IHC
EGFR T790M	Pre-screening	Tumor (preferably same specimen as for MET)	Central: PCR
[redacted]			

Biomarker	Time point	Sample	Method
Cell-free DNA	Screening or C1D1 (pre-dose), C3D1 and every 3rd cycle, EOT	Blood	Central: PCR, NGS and/or other methods

[redacted]

2.11.4 General data handling and preprocessing

Refer to Section 2.1.4 for the baseline definition.

Data preprocessing and transformations are described in detail in the Programming Dataset Specifications document.

Samples for biomarkers were either analyzed locally (activating mutations and some MET and EGFR T790M status in Phase Ib) or by a central laboratory. There are therefore 2 sources of biomarker data, the eCRF and data provided by one or more vendors. The B1 domain will contain the data from all sources and the origin is specified in the data.

In general the INC280 project standard will be applied, i.e. central data will be prioritized when local results are also available. Depending on the actual data the following rules will also be applied, if necessary:

- Both scheduled and unscheduled visits will be taken into account

If a central result is available it will be used (prioritized over local), otherwise the/a local result; see details in the below Table 2-9 for the resistance mechanism analysis (T790M and MET) in Phase Ib. Per protocol, a central result is required for subjects in Phase II (see Table 2-8); in case there is no valid central result but a local result with the appropriate test method, Table 2-9 will also be applied for Phase II.

- In general the latest assay date per parameter (i.e. closer to treatment start date) will be used if results for several dates are available and the results for the latest date are reported (i.e. 'REPORTED RESULT') and not 'Unknown'; otherwise ('NOT ANALYZED' or similar cases), a valid result from an earlier assay date will be used if one is available.

[redacted]

- For the resistance mechanism, only results from test methods specified in Table 2-7 and Table 2-8 should be used, i.e.
  - MET: FISH, IHC, or any method for local testing in Phase Ib; FISH and/or-IHC for central testing in Phase Ib; FISH and/or-IHC for central testing in Phase II;
  - EGFR T790M: Qiagen therascreen (PCR) or Roche Cobas (PCR) (all countries except USA) for local testing in Phase Ib; PCR for central testing in Phase Ib; PCR for central testing in Phase II.

Table 2-9 Prioritization of biomarker results from different sources for resistance mechanism analysis in Phase Ib subjects

Central test result	Local test result				
	Mutant	Non-mutant	Unknown	Not analyzed/ analyzable	No result available
Mutant	Mutant	Mutant	Mutant	Mutant	Mutant
Non-mutant	Non-mutant	Non-mutant	Non-mutant	Non-mutant	Non-mutant
Unknown	Mutant	Non-mutant	Unknown	Unknown	Unknown
Not analyzed/ analyzable	Mutant	Non-mutant	Unknown	Unknown	Unknown
No result available	Mutant	Non-mutant	Unknown	Unknown	Unknown

Immunohistochemistry data

Immunohistochemistry (IHC) data reported from the lab will include quantitative data such as percent tumor and percent positive cells or a semi quantitative measure of protein expression. The pathologist determines whether the staining is absent (0+), slight (1+), moderate (2+), or strong (3+). The histoscore (H-score) is then calculated as the sum of (the percentages of stained cells × their intensity), or (%1+ × 1) + (%2 + × 2) + (%3 + ×3), and ranges between 0 and 300.

FISH data

Fluorescent In Situ Hybridization (FISH) data will include data on DNA copy numbers. The average gene copy number (GCN) will be used.

PCR data

Polymerase chain reaction (PCR) data to assess mutations of the epidermal growth factor receptor (EGFR) will include categorical data on mutations in different exons.

2.11.5 Derivation of resistance mechanism subgroups

[redacted], biomarkers are also analyzed to assign subjects in Phase Ib and Phase II to a category of the subgroups MET dysregulation status, T790M mutation status, and T790M & MET status (see Section 2.2.2.1). The resistance mechanism subgroups will be summarized by means of a frequency table (T790M & MET status) and a contingency table (MET dysregulation status vs T790M mutation status) by treatment group. Percentages will be calculated using the number of subjects in the relevant analysis set or subgroup as the denominator.

MET dysregulation status

The IHC and/or FISH results [redacted] will be used to determine the MET status of the subject. The subgroup categories will be assigned as follows:

- Missing, if no results are available or the available results are not sufficient (i.e. both GCN and staining category missing, MET?)
- MET dysregulated (MET+), if staining category = 3+ (defined as ≥ 50% of cells staining with high intensity) or average gene copy number ≥ 4 (or both)
- MET not dysregulated (MET−), otherwise

T790M mutation status

The EGFR mutation results [redacted] will be used to determine the T790M status of the subject. The subgroup categories will be assigned as follows:

- T790M+, if the T790M mutation is reported [redacted]
- T790M−, if it is reported that a T790M mutation was not found [redacted]
- T790M?, if the test result is reported as Unknown, Not evaluable, or Not analyzed/analyzable or is completely missing

Please also see Section 4.

T790M & MET status

The subgroups of combined and marginal T790M and MET status will be determined from the above MET dysregulation and T790M mutation status:

T790M+ & MET+	T790M+ & MET−	T790M+ & MET?
T790M− & MET+	T790M− & MET−	T790M− & MET?
T790M? & MET+	T790M? & MET−	T790M? & MET?
T790M+	T790M−	T790M?
MET+.	MET−	MET?

Only categories present in the data will be presented and not all categories might be presented in all outputs (e.g. in-text outputs).

MET amplification status

Categories for MET amplification status, i.e. GCN alone, are:

- <4
- 4–6
- ≥ 6
- failed or missing

The failed or missing category might not be presented in all outputs.

MET expression status

Categories for MET expression status, i.e. IHC staining category alone, are:

- 0+
- 1+
- 2+
- 3+
- failed or missing

The failed or missing category might not be presented in all outputs.

2.11.6 Biomarker analysis

Unless otherwise specified, the analyses will be presented separately for Phase Ib and Phase II subjects.

[redacted]

2.12 Other exploratory analyses

Not applicable.

2.13 Interim analysis

2.13.1 Phase Ib part

No formal interim analyses are planned. However, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose-escalation part, the next dose will be chosen depending on the observed data. Details of this procedure and the process for communication with investigators are provided in [CSP Section 6.2.3].

2.13.2 Phase II part

The futility interim analysis was conducted for subjects enrolled in Group 3 (EGFRmut, T790M negative, any MET, 1L antineoplastic) with 21 subjects who had completed at least 4 cycles of treatment or discontinued treatment prior to that time (see [primary CSR] for details and results).

3 Sample size calculation

Please refer to the [Primary CSR] for details about sample size calculations.

4 Change to protocol specified analyses

[redacted]

Hepatotoxicity

To implement the Novartis Hepatotoxicity Guideline released in 2019, the analysis of liver function parameters was modified accordingly.

COVID-19

Analysis of protocol deviations related to COVID-19 were added.

Imputation rules

Imputation rules for partial dates of anti-cancer therapies were updated.

5 Appendix

5.1 Imputation rules

5.1.1 Investigational drug

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

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

The subject should be treated as on-going and the cut-off date should be used as the dose end date. Scenario 1 should not be applicable for the final CSR. All subjects in the current analysis have the EOT page completed before DBL for the final CSR.

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)

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

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

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

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

5.1.2 AE 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

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 and 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 and end date of the on-treatment period *

Missing element	Rule

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

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

Any AEs and concomitant 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.

5.1.3 Other imputations

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

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 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 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, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between the previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

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

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 the 15th day of the month and year of death

- If both day and month are missing, then impute 01Jul of the year of death

Prior antineoplastic therapies date imputation

- Start dates
  The same rule which is applied to the imputation of AE/concomitant medication start dates will be used with the following exception:
  - If month and day are missing and the available year = year of study treatment start date, then impute with study treatment start date − 1
- End dates
  - If day is missing, imputed date = min(reference end date, last day of the month)
  - If month and day are missing, imputed date = min(reference end date, 31Dec)

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.

Post-treatment antineoplastic therapies date imputation

For new antineoplastic (ANP) therapies starting after study treatment was discontinued or starting while study treatment was still ongoing (protocol deviation), a missing or partial start date of this new therapy will be imputed as specified in Table 5-3.

The complete (imputed) dates are required for censoring of efficacy endpoints. Therefore, partial or missing start dates will only be imputed for the first such therapy. Partial or missing end dates of the first new therapy and any partial or missing dates of second or later new antineoplastic therapies will not be imputed.

Table 5-3 Imputation of start dates for post-treatment antineoplastic medications

Missing element	Rule
Day	• If available year ≥ year of study treatment end date then ANP start date = max (study treatment end date + 1, 01MonYYYY) • If available year < year of study treatment end date then ANP start date = max(study treatment start date + 1, 01MonYYYY)

Day, month	• If available year = year of study treatment end date then ANP start date = min(study treatment end date + 1, 31DecYYYY)
	• If available year > year of study treatment end date then ANP start date = 01JanYYYY
	• If available year < year of study treatment end date,
	  • If available year < year of study treatment start date, do not impute
	  • If available year > year of study treatment start date, then ANP start date = 01JulYYYY
	  • If available year = year of study treatment start date and day/month of study treatment start date <01JulYYYY, then ANP start date = 01JulYYYY

Missing element	Rule
	• If available year = year of study treatment end date and day/month of study treatment start date ≥ 01JulYYYY, then ANP start date = min(middle between the treatment start and end date, 31DecYYYY)
Day, month, and year	For completely missing start dates, set to study treatment end date + 1

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.

In case there are any scenarios found in the final data that are not covered by the rules above, they will be handled in the respective dataset program and documented in the PDS.

5.2 AE coding/grading

Adverse events are coded using the MedDRA terminology. The latest available MedDRA version at the time of the analyses will be used and the version will be specified in the CSR as well as in a footnote in the applicable tables and listings.

AEs will be assessed according to CTCAE version 4.03.

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 CTCAE version 4.03. 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 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 4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE version 4.03, 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 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.

5.3.2 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 an xxx differential:

xxx count = (WBC count) × (xxx %value / 100).

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

Corrected Calcium (mg/dL) = Calcium (mg/dL) − 0.8 × [Albumin (g/dL) − 4].

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

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

5.4 Statistical models

5.4.1 Phase Ib

Refer to the [Primary CSR] for details.

Kaplan-Meier estimates

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

Median survival for each treatment group, subgroup or overall 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 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated ([Clopper and Pearson 1934]).

6 References

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

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

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

European Medicines Agency (2021). Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic (Version 4.0).

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