NOVARTIS

Clinical Development

INC280/capmatinib

CINC280A2201/ NCT02414139

A phase II, multicenter, study of oral cMET inhibitor INC280 in adult patients with EGFR wild-type (wt), advanced non-small cell lung cancer (NSCLC)

Statistical Analysis Plan for Final CSR (End of Study)

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1.0	03-Mar-2023	Initial version for the final CSR

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1 Introduction

This Statistical Analysis Plan (SAP) describes the planned statistical methods for all safety, efficacy, pharmacokinetic, [redacted] analyses for study CINC280A2201. This SAP refers to study protocol amendment 6.

1.1 Study design

This is a prospectively designed, multicenter, open-label, phase II study to evaluate the efficacy and safety of single-agent INC280. NSCLC patients with stage IIIB or IV that are EGFR wild-type (for exon 19 deletions and exon 21 L858R substitution mutations) and ALK-negative rearrangement will be pre-screened for MET amplification and MET mutation status. Enrolled patients will be assigned to the following nine cohorts:

- Cohort 1: Pre-treated patients with MET GCN ≥ 6, including:
  - Cohort 1a: Patients with a MET GCN of ≥ 10, or
  - Cohort 1b: Patients with a MET GCN of ≥ 6 and < 10, or
- Cohort 2: Pre-treated patients with MET GCN ≥ 4 and < 6, or
- Cohort 3: Pre-treated patients with MET GCN < 4, or
- Cohort 4: Pre-treated patients with MET mutations regardless of MET GCN, or
- Cohort 5: Treatment-naïve patients with MET dysregulation, including:
  - Cohort 5a: Patients with a MET GCN ≥10, or
  - Cohort 5b: Patients with MET mutations regardless of MET GCN
- Cohort 6: Pre-treated patients with either MET GCN ≥ 10 without MET mutations or MET mutations regardless of MET GCN
- Cohort 7: Treatment-naïve patients with MET mutations regardless of MET GCN

Primary diagnostic of MET amplification (and ALK rearrangement, if applicable) will be performed using fluorescence in situ hybridization (FISH) and for MET mutations by RT-PCR at a Novartis-designated central laboratory. [redacted]

Enrolled patients will be treated with INC280 tablets at 400 mg twice daily (BID). Treatment with INC280 will continue until patient experiences any of the following: disease progression according to RECIST 1.1 as determined by investigator and confirmed by BIRC, unacceptable toxicity that precludes further treatment, treatment is discontinued at the discretion of the Investigator or patient, lost to follow-up, or death. Treatment with INC280 may be continued beyond RECIST 1.1-defined PD (as determined by investigator and confirmed by BIRC) if, in

the judgment of the investigator, there is evidence of clinical benefit and the patient wishes to continue on the study treatment.

Approximately 456 patients (69 patients per each Cohort 1a, 1b, 2, 3, 4; 27 patients per each Cohort 5a, 5b; approximately 30 patients in Cohort 6 and approximately 27 patients in Cohort 7) were to be enrolled in the study if none of the five cohorts (Cohort 1a, 1b, 2, 3, 4) are stopped for futility at the time of the interim analysis. No interim analysis is planned for Cohorts 5a, 5b, 6 and 7.

The primary analysis will be conducted when all treated patients in their respective cohort (if not stopped for futility at interim analysis) have completed at least 6 cycles of treatment (18 weeks) or discontinued treatment earlier. Due to the expected difference in enrollment rate for each cohort, the primary analysis for the different cohorts may occur at different times. The primary analysis for any cohort that was stopped for futility may be combined with the primary analyses for other cohorts. Also, if majority of the patients in a cohort meet the required follow-up time for primary analysis, the primary analysis of such cohorts may be combined with the primary analyses for other cohorts.

1.2 Objectives

1.2.1 Primary objective

The primary objective is to evaluate the antitumor activity of INC280, as measured by overall response rate (ORR) by Blinded Independent Review Committee (BIRC) assessment, by cohort.

1.2.2 Secondary objectives

Key secondary objective is to evaluate duration of response (DOR) as assessed by BIRC, by cohort.

Other secondary objectives are:

- To evaluate ORR and DOR by investigator assessment, by cohort
- To evaluate time to response (TTR), disease control rate (DCR) and progression-free survival (PFS) by investigator and by BIRC assessment, by cohort
- To evaluate overall survival (OS), by cohort
- To evaluate INC280 safety profile as monotherapy in NSCLC patients with advanced/metastatic setting
- To characterize the pharmacokinetics of INC280 and metabolite CMN288

2 Statistical methods

This section and its subsections will be imported to section 9.7 of the CSR after the analyses have been conducted. This section of the SAP follows the CSR template structure of Section 9.7 as of the release date of this document.

The text will be changed to the past tense when imported into the CSR; references to Section 4 of the SAP, where additional details are provided for programming implementation, may be removed in the CSR.

In what follows, study drug refers to INC280.

2.1 Data analysis general information

Data will be analyzed by Novartis Biostatistics and Statistical Programming personnel according to the data analysis section 10 of the CINC280A2201 protocol, which will be available in Appendix 16.1.1 of the Clinical Study Report (CSR). Important information is given in the following sections and details are provided, as applicable, in Section 4 from which Appendix 16.1.9 of the CSR will be extracted.

SAS® version 9.4 (or later version if available at time of database lock) will be used in all analyses.

Data from all patients who signed informed consent in centers that participate in this study will be used in the analysis. Data collected after withdrawal of informed consent will not be reported. Data collected on the same date as withdrawal of informed consent are reported. Due to expected small size of enrollment at individual centers, no center effect will be assessed. Each analysis will use all data in the database up to the analysis cutoff date, determined prior to database lock.

The data from all participating centers in this protocol will be combined. For cohorts 1-4, the efficacy data for each cohort will be analyzed separately at the time of the interim analysis and one (or more) of the cohorts may be stopped for futility according to the criteria described in the Interim Analysis Section of the study protocol (Section 10.7). No interim analysis for futility is planned for Cohorts 5a, 5b, 6 and 7.

Previous reports

- The primary analyses for MET mutant patients (Cohort 4, and 5b) and for all closed cohorts for futility (Cohorts 1b, 2, and 3) were conducted based on data with a data cut-off date of 15-Apr-2019.
- The primary analyses for MET amplified patients with a MET GCN ≥ 10 (Cohorts 1a and 5a) and pre-treated expansion cohort (Cohort 6) were conducted based on data with a data cut-off date of 06-Jan-2020.
- A preliminary analysis for MET mutant patients (expansion Cohort 7) along with updated results from other MET mutant cohorts (Cohorts 4, 5b and 6) was conducted based on data with a data cut-off date of 18-Sep-2020.
- The primary analyses for MET mutant patients (expansion Cohort 7) along with updated results from other MET mutant cohorts (Cohorts 4, 5b and 6) was conducted based on data with a data cut-off date of 30-Aug-2021.

Planned analyses for this report

- The updated analyses for **all MET mutant patients (**Cohorts 4, 5b and 6, and 7) will be conducted when Last Patient Last Visit is reached.
- Data from cohorts (Cohort 1-7) will be included for patient disposition, baseline characteristics and safety analyses. Patient disposition, baseline characteristics and safety analyses will also be presented combining the MET mutant patients (pre-treated, treatment-naïve and all MET mutant patients) and all amplified patients (complementary subgroup to MET mutant patients).
- Data from MET mutant cohorts (Cohort 4, 5b, 6 and 7) will be included for efficacy a[redacted] They will also presented combining the MET mutant patients (pre-treated and treatment-naïve MET mutant patients).
- No PK analyses will be included in this report as no additional PK samples are analyzed at this time.

[redacted]

All available data from all patients will be summarized in the final Clinical Study Report (CSR).

Section 4.1 provides further details regarding data to be included in the analyses.

General presentation of descriptive summaries

Qualitative data (e.g., gender, race) will be summarized by frequency counts and percentages. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

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

2.2 Analysis sets

Screened patients

Patients are considered to be enrolled into the study if they have signed main informed consent. Only patients who have signed main informed consent will be included in the analysis data sets.

Patients are considered to be a screen failure if they have signed main informed consent but failed to be treated.

Patients are considered to be a pre-screen failure if they have failed to meet pre-screened criteria i.e. they have not signed main informed consent.

Full Analysis Set

The Full Analysis Set (FAS) includes all patients who received at least one dose of INC280. The FAS will be used for all listings. Unless otherwise specified the FAS will be the default analysis set used for all efficacy analyses.

Safety Set

The Safety Set includes all patients who received at least one dose of INC280. All safety data will be analyzed using the Safety Set.

The FAS and Safety Set in this study are identical.

Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of patients in the FAS who have no major protocol deviations, regardless of the adequate tumor assessment.

The major protocol deviations that will lead to removal of patients from the PPS are listed below:

- Patient does not have Stage IIIB or IV NSCLC (any histology) at the time of study entry
- Patient does not have a histologically or cytologically confirmed diagnosis of non-squamous NSCLC with EGFR wt status (for exon 19 deletions and exon 21 L858R substitution mutations)
- Patient with NSCLC of pure squamous cell histology that has known EGFR mutations in exons 19 or 21 is enrolled
- Patient without MET status for eligibility as determined by central assessment at a Novartis designated laboratory prior to first dose
- Patient has not received one or two prior lines of systemic therapy for advanced/metastatic disease (only for cohorts 1a, 1b, 2, 3 and 4)
- Patient has received prior systemic therapy for advanced/metastatic disease (only for cohorts 5a and 5b and 7)
- Patient has not received one prior line of systemic therapy for advanced/metastatic disease (only for cohort 6)
- Patients has no measurable lesion from RECIST 1.1 evaluation at baseline or has no baseline evaluation

- Patient has received crizotinib, or any other MET or HGF inhibitor before entering screening
- Patient has characterized ALK-positive rearrangement or un-determinant ALK rearrangement status at study entry
- ECOG performance status > 1 at study entry
- Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type

Combined cohorts

Patient disposition, baseline characteristics, exposure and safety analyses will be presented combining the MET mutant cohorts per line of treatment and regardless of the line of treatment, and all amplified cohorts whereas [redacted] efficacy will be presented combining the MET mutant cohorts per line of treatment.

The combined cohorts are defined as follows:

- *All patients (2/3L, MET mutant) (N=100):* Pretreated patients from Cohort 4 and subset of MET mutant patients from Cohort 6.
- *All patients (1L, MET mutant) (N=60):* Treatment-naïve patients from Cohort 5b and 7.
- *All MET mutant patients (N=160):* All MET mutant patients regardless of the line of treatment i.e. Pre-treated MET mutant patients (2/3L, MET mutant) and treatment-naïve MET mutant patients (1L, MET mutant) as defined above.
- *All Amplified patients (N=213):* All patients enrolled in cohorts other than MET mutant cohorts (Cohorts 1a, 1b, 2, 3, 5a and subset of amplified patients from Cohort 6).
- All patients (N=373): All patients enrolled in the study.

Subgroup analysis

Efficacy

ORR, DOR, PFS by BIRC and investigator assessment will be summarized for the following subgroups:

- age group (< 65 years, ≥ 65 years)
- gender (male, female)
- race (Caucasian, Asian, Others)
    - *Others: include Black, Other, Unknown, Native American*
- ECOG performance status (0, ≥1)

Safety

Adverse events (AEs) will be summarized for the following subgroups:

- age group (< 65 years, ≥ 65 years)
- gender (male, female)
- race (Caucasian, Asian, Others)
- ECOG performance status (0, ≥1)
- Patients with long exposure of study drug (at least 48, 72, 96 weeks of exposure)

2.3 Patient demographics and other baseline characteristics

The FAS will be used for all patient demographic and baseline characteristic summaries and listings.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by cohort. Categorical data (e.g. gender, race, ethnicity, ECOG performance status) will be summarized by frequency count and percentages. Continuous data (e.g. age, weight, height, BMI) will be summarized by descriptive statistics (as defined in Section 2.1).

Diagnosis and extent of cancer

Descriptive statistics and frequency counts and percentages will be tabulated by cohort, as appropriate, for diagnosis and extent of cancer based on the data collected on the electronic Case Report Form (eCRF) including: primary site of cancer, tumor histology/cytology, histological grade, time (in months) since initial diagnosis of primary site, stage at initial diagnosis, time (in months) from initial diagnosis to first recurrence/progression, time (in months) since most recent relapse/progression, current extent of disease (metastatic sites), number of metastatic sites at baseline, types of lesions (target and non-target lesions) at baseline, number of target lesions at baseline, and disease burden at baseline for target lesion (based on the data collected on the RECIST eCRF page).

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms will be summarized and listed by cohort. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class and preferred term. Medical history and current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Prior anti-cancer therapy

Prior anti-neoplastic (anti-cancer) therapy will be listed in three separate categories by cohort: 1. medications, 2. radiotherapy, and 3. surgery.

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

Prior anti-neoplastic medications will be summarized by chemotherapy (medication) setting, other therapy (medication) setting, number of prior regimens of anticancer medications and

prior anticancer medications. Prior antineoplastic medications will also be summarized by ATC class, and preferred term. The medication therapy type of any combination therapy will be classified based on the following order: immunotherapy, chemotherapy, biologic therapy (other than immunotherapy), targeted therapy, hormonal therapy. For example, a combination therapy of chemotherapy and immunotherapy will be classified as 'immunotherapy'.

Prior anti-neoplastic systemic medications (any line, 1st line, 2nd line) will be summarized by line: single agent chemotherapy, Platinum based chemotherapy, immunotherapy.

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

2.4 Protocol deviations

In addition to the pre-defined standard PD terms, new protocol deviations and the corresponding relationship (health status related, lockdown/quarantine of patient, site issues, patient concerns, etc.) to the COVID-19 pandemic in line with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (March 2020) and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" (February 2021) from EMA were defined.

Frequency counts and percentages of patients in the FAS with any protocol deviations (related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be tabulated by deviation category and cohort, broken down by COVID-19 relationship (COVID-19 related PDs or not). Major protocol deviations will be tabulated separately by cohort. A cross-tabulation of COVID-19 related protocol deviations vs. corresponding COVID-19 situation will also be produced by cohort. All protocol deviations will be listed by cohort.

2.5 Patient disposition

The FAS will be used for the patient disposition summary tables by cohort. The FAS will be used for the listings by cohort.

The following will be tabulated:

- Number (%) of patients who are still on-treatment (based on the absence of the 'End of Treatment Phase Disposition' page);
- Number (%) of patients who discontinued treatment (based on completion of the 'End of Treatment Phase Disposition' page with date of discontinuation and reason of discontinuation/ 'Subject Status' entered);
- Number (%) of patients who entered post treatment efficacy follow-up (based on 'Next Phase Entered' is 'Post-treatment follow-up' on the 'End of Treatment Phase Disposition' page for patients who discontinued treatment);
- Number (%) of patients who entered survival follow-up (based on 'Next Phase Entered' is 'Survival follow-up' on the 'End of Treatment Phase Disposition' page for patients who discontinued treatment);

- Number (%) of patients who discontinued from study (based on 'Will subject continue into the next phase of the trial' is 'No' as entered on the 'End of Treatment Phase Disposition' page for patients who discontinued treatment);
- Primary reasons for study treatment discontinuation (based on discontinuation reasons entered under 'Subject Status' in the 'End of Treatment Phase Disposition' page);
- Number (%) of patients who are still in the post-treatment study phase (based on presence of 'End of Treatment Phase Disposition' and absence of 'Study Phase Disposition' page);
- Number (%) of patients who discontinued from the post-treatment efficacy follow-up (based on completion of 'Study Phase Disposition' page with date of discontinuation and discontinuation reasons entered under 'Subject Status');
- Number (%) of patients who entered survival follow-up (based on completion of 'Study Phase Disposition' page with date of discontinuation and discontinuation reasons entered under 'Subject Status' and 'Next Phase Entered' is 'Survival follow-up' for patients who discontinued from the post-treatment efficacy follow-up);
- Number (%) of patients who discontinued from study (based on completion of 'Study Phase Disposition' page with date of discontinuation and discontinuation reasons entered under 'Subject Status' and 'Will subject continue into the next phase of the trial' is 'No' for patients who discontinued from the post-treatment efficacy follow-up);
- Primary reasons for discontinuation from the post-treatment efficacy follow-up (based on discontinuation reasons entered under 'Subject Status' in the 'Study Phase Disposition' page).

Note: 'Study Phase Disposition' page corresponds to 'End of Post-Treatment disposition' CRF page.

2.6 Treatments (study drug, concomitant therapies, compliance)

The Safety Set will be used for all medication data summaries and listings unless otherwise specified.

Study drug and study treatment

Study drug and study treatment both refer to INC280 and will be used interchangeably.

Date of first/last administration of study drug

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug was administered and recorded on the Dosage Administration Record (DAR) eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred to as start date of study drug.

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on DAR eCRF. This date will also be referred to as last date of study drug.

Study day

The study day for all assessments (e.g. tumor assessment, death, disease progression, tumor response, performance status, adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption) will be calculated using the start date of study drug as the origin. For assessments occurring after or on the start date of study drug, study day will be calculated as:

Study Day =Event date - start date of study drug + 1.

The first day of study drug is therefore study day 1.

For any assessment or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) occurring prior to the start of the study drug, study day will be negative and will be calculated as:

Study Day = Event date - start date of study drug.

The study day will be displayed in the relevant data listings.

Dose exposure and intensity

Definitions of duration of exposure, cumulative dose, average daily dose, dose intensity (DI), relative dose intensity (RDI), as well as intermediate calculations, include:

- Duration of exposure (days): last date of study drug − first date of study drug + 1 (periods of interruption are not excluded)
- Cumulative dose (mg): total dose of study drug taken by a patient in the study
- Number of dosing days (days): duration of exposure − number of zero dose days
- Average daily dose (mg/day): cumulative dose (mg)／number of dosing days (days)
- DI (mg/day): cumulative dose (mg)／duration of exposure (days)
- RDI (%): 100 × [DI (mg/day)／planned dose (800 mg/day)]

Note: Because the planned INC280 dose is 800 mg/day, or the planned dose intensity (PDI) is 800 mg/day, RDI (%) can be calculated by 100*DI/PDI and simplified as shown above.

Duration of study exposure to study drug, cumulative dose, average daily dose, DI and RDI will be summarized by cohort. In addition, the duration of exposure to study drug will be categorized into time intervals and frequency counts and percentages of patients with exposure in each time interval will be presented. Frequency counts and percentages of patients who have dose changes, reductions or interruptions, and the corresponding reasons, will be summarized by cohort.

An analysis of time to first interruption (in weeks) will be presented based on simple descriptive statistics (not using time-to event methods).

Time to first interruption is the time from date of first administration of study drug to the first date when a zero dose of study drug is recorded on the DAR eCRF, expressed in weeks. Listings of all doses of the study drug along with dose change and dose interruption reasons will be produced by cohort.

Section 4.5 provides further details on the definition of dose changes and interruptions.

Concomitant therapy

Concomitant therapies are defined as any medications (excluding study drug, prior antineoplastic treatments and blood transfusions), surgeries or procedures (including physical therapy) administered in the study and are recorded in the Prior and Concomitant Medications and the Surgical and Medical Procedures eCRF, respectively.

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

Concomitant therapies will be summarized by ATC class, preferred term and cohort. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include: 1) medications starting on or after the start of study drug but starting no later than 30 days after last dose of study drug and 2) medications starting prior to the start of study drug but continuing after the start of study drug.

All concomitant therapies will be listed by cohort. Any concomitant therapies starting and ending prior to the start of study drug or starting more than 30 days after the last date of study drug will be flagged in the listings.

Antineoplastic therapy after discontinuation of study drug

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

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

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

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

2.7 Analysis of the primary variable

The primary objective is to demonstrate the antitumor activity of INC280, as measured by overall response rate (ORR) to INC280 by Blinded Independent Review Committee (BIRC) assessment, by cohort.

2.7.1 Variable

The primary variable used to evaluate the anti-tumor activity of INC280 is the overall response rate (ORR), defined as the proportion of patients with a best overall response (BOR) as complete response (CR) or partial response (PR), as assessed per RECIST 1.1 by BIRC.

Best overall response (BOR)

The BOR will be assessed based on reported lesion responses at different evaluation time points. Both CR and PR must be confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met. The next scheduled assessment may be used for purposes of confirmation of response.

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

- CR = at least two determinations of CR at least 4 weeks apart before progression
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR)
- SD = at least one SD assessment (or better) > 6 weeks after start of study drug (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after start of study drug (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks)

Only tumor assessments performed before the start of any further anti-neoplastic therapies (i.e. any additional secondary anti-neoplastic therapy or anti-cancer surgery) and within 30 days after the last dose of study treatment will be considered in the assessment of BOR.

Local bone radiotherapy for analgesic purposes or for lytic lesions at risk of fracture are not considered secondary anti-neoplastic therapy. If a patient receives any further anti-neoplastic therapy while on study, any subsequent assessments will be excluded from the BOR determination. Further anti-neoplastic therapies will be identified via protocol deviations or from the data collected on 'Anti-neoplastic therapies since last date of study drug' as appropriate. Palliative radiotherapy in the bone is the only setting of radiotherapy allowed during the study. Therefore palliative radiotherapy in the bone will not be considered as an anti-neoplastic therapy for assessment of BOR.

Clinical deterioration will not be considered as documented disease progression.

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

- No valid post-baseline assessment
- All post-baseline assessments have overall response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- Stable disease (SD) too early (≤ 6 weeks after start date of study drug*)
- PD too late (> 12 weeks after start date of study drug*)

Special (and rare) cases where BOR is 'unknown' due to both early SD and late PD will be classified as 'SD too early'.

*Thresholds for SD too early and PD too late are defined as the protocol-specified time interval + protocol-allowed time windows (±4 days) around the tumor assessments.

2.7.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be performed on the FAS. The primary efficacy endpoint ORR will be estimated and the exact 95% confidence interval (CI) (Clopper and Pearson 1934) provided by cohort.

Treatment with INC280 will be considered to have clinically relevant efficacy in cohort (1-4) if an ORR of ~35% is observed in that cohort with lower bound of exact 95% CI greater than 25%. Whereas, in cohorts (5a and 5b and 7), treatment with INC280 will be considered to have clinically relevant efficacy if an ORR of ~55% is observed in that cohort with lower bound of exact 95% CI greater than 35%.

No hypothesis testing is planned for cohort 6.

2.7.3 Handling of missing values/censoring/discontinuations

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

Patients with a BOR of 'Unknown' per RECIST 1.1 will be considered as non-responders when estimating ORR.

Patients with no BIRC data will be considered as non-responders when estimating ORR.

Patients who have disease progression and continue to receive study drug after progression will qualify for PD at the time of progression and will be counted as PD in the derivation of ORR and any other efficacy endpoints.

2.7.4 Supportive analyses

ORR by BIRC will be presented combining the MET mutant cohorts per line of treatment as defined in Section 2.2.

ORR by BIRC will be summarized by subgroup (as defined in Section 2.2). Forest plot (including sample size/number of responders and ORR with 95% CI) will be produced to graphically depict the treatment effect estimates in different subgroups.

In addition, the primary analysis will be repeated on the PPS.

Waterfall plots representing the best percentage change from baseline in the sum of the tumor measured diameters for target lesions will be produced by cohort.

ORR by BIRC according to the accepted radiologist who was chosen at the time of the submission will be produced as per FDA request (Previous Radiologist Accepted flag: PRARDF): radiologist chosen at the data cut-off 15-Apr-2019 for NDA submission in Cohorts 4 and 5b and at the data cut-off 30-Aug-2021 for Post-Marketing Requirements (PMR) in Cohorts 6 and 7.

2.8 Analysis of secondary variables

2.8.1 Efficacy

All secondary endpoint analyses will be performed based on the FAS, unless otherwise specified. Efficacy will also be presented combining the MET mutant cohorts per line of treatment as defined in Section 2.2.

No adjustment for multiple testing will be made.

Key secondary efficacy endpoints

The key secondary objective is to evaluate duration of response (DOR) as assessed by BIRC, by cohort.

Among patients with a confirmed response (PR or CR), DOR is defined as the time from first documented response (PR or CR) to the date of first documented PD or death due to any cause. If a patient has not had an event, DOR is censored at the date of last adequate tumor assessment.

The censoring and event date options to be considered for the main analysis are presented in Table 2-1.

Table 2-1 Outcome and event dates for DOR and PFS analyses

	Situation	Date	Outcome
A	No baseline assessment	Date of first dose of study drug [a]	Censored
B	Progression at or before next scheduled Assessment	Date of progression	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate assessment	Censored
D	No progression	Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A	Information ignored. Outcome derived based on radiology data only.
F	New anticancer therapy given	Ignore the new anticancer therapy and follow situations above	As per above situations
G	Deaths due to reason other than deterioration of 'Study indication'	Date of death	Progressed

[a] The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death

DOR will be described in tabular and graphical format using Kaplan-Meier methods. The Kaplan-Meier estimate of the distribution function will be constructed. Kaplan-Meier curves

will be constructed. The number of patients at risk at certain time points will be shown on the plot. The estimated median (in months) along with 95% CIs, as well as 25th and 75th percentiles will be reported (Brookmeyer and Crowley 1982). In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points (including at least 3, 6, 12, and 18 months) will be summarized. Refer to Section 4.6.3 for further details regarding derivation of Kaplan-Meier estimates.

Supportive analysis

DOR by BIRC will also be presented combining the MET mutant cohorts per line of treatment as defined in Section 2.2.

DOR by BIRC assessment will be summarized by subgroup (as described in Section 2.2).

Supportive analysis of DOR table by BIRC assessment based on the PPS will also be presented.

DOR by BIRC according to the accepted radiologist who was chosen at the time of the submission will be produced as per FDA request (Previous Radiologist Accepted flag: PRARDF): radiologist chosen at the data cut-off 15-Apr-2019 for NDA submission in Cohorts 4 and 5b and at the data cut-off 30-Aug-2021 for Post-Marketing Requirements (PMR) in Cohorts 6 and 7.

ORR by investigator assessment

The evaluation of ORR will be also conducted based on investigator assessment. ORR will be estimated and the exact binomial 95% CI will be provided by cohort.

ORR by investigator will be summarized by subgroup (as defined in Section 2.2) and forest plot will be produced.

A summary table will also be produced for BOR based on investigator assessment versus BIRC assessment. An assessment of the concordance between BIRC assessment and local assessment of the Best Overall Response for each patient will be provided by cohort. Overall concordance rate in each cohort is calculated as (number of patients with same BORs per investigator and per BIRC)/(total number of patients in that cohort).

DOR by investigator assessment

Among patients with a confirmed response (PR or CR), DOR is defined as the time from first documented response (PR or CR) to the date of first documented PD or death due to any cause. If a patient has not had an event, DOR is censored at the date of last adequate tumor assessment.

The censoring and event date options to be considered for the main analysis are presented in Table 2-1.

DOR will be described in tabular and graphical format using Kaplan-Meier methods by cohort. The Kaplan-Meier estimate of the distribution function will be constructed. Kaplan-Meier curves will be constructed. The number of patients at risk at certain time points will be shown on the plot. The estimated median (in months) along with 95% CIs, as well as 25th and 75th percentiles will be reported (Brookmeyer and Crowley 1982). In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points (including at least 3, 6, 9, 12 and 18 months) will be summarized by cohort. These analyses will be performed

separately based on BIRC assessment and based on investigator assessment. Refer to Section 4.6.3 for further details regarding derivation of Kaplan-Meier estimates.

Disease control rate (DCR)

DCR is defined as the proportion of patients with best overall response of CR, PR, or SD per RECIST 1.1. DCR will be estimated and the binomial exact 95% CI will be provided by cohort. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

Time to response (TTR)

TTR is defined as the time from start of study drug to first documented response (CR or PR, which must be confirmed subsequently) for patients who achieved a confirmed PR or CR. All patients in the FAS will be included in time to response calculations. Patients who did not achieve a confirmed PR or CR, will be censored at:

- the maximum follow-up time (i.e. first patient first treatment to last patient last treatment by cohort used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause), or at the date of last adequate tumor assessment date otherwise.

TTR will be summarized in 6-weeks intervals using descriptive statistics. The distribution of time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. Failure curves (ascending Kaplan-Meier curves) will be constructed. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

Progression-free survival (PFS)

PFS is defined as the time from the start date of study drug to the date of the first radiologically documented PD or death due to any cause.

If a patient has not progressed or is not known to have died at the date of analysis cut-off, PFS will be censored at the date of the last adequate tumor evaluation before the cut-off date. PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1 documented disease progression or death) will be considered for the primary analysis provided tumor assessments continue after initiation of the new cancer therapy. Clinical deterioration will not be considered as a qualifying event for progression. Refer to Table 2-1 for censoring and event date options and outcomes for PFS.

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 two or more missing tumor assessments (see Section 4.6.1). See also Section 4.6.1 describing the special case of a missing baseline tumor assessment.

Patients with no BIRC data will be considered censored at the start date of study drug.

PFS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR by cohort, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several

time points. Censoring reasons will also be summarized by cohort. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

In addition, PFS table will be repeated on the PPS.

Overall survival (OS)

OS is defined as the time from the start date of study drug to the date of death due to any cause. If the patient is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cutoff date (see Section 4.3 for further details on derivation of last contact date).

OS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR by cohort, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points . Censoring reasons will also be summarized by cohort.

OS from initial diagnosis to the date of death due to any cause will also be analyzed. Date of censoring is the same as defined for OS analysis.

Duration of Follow-up

Follow-up in the study will be summarized using the following methods to provide a comprehensive assessment of follow-up for all patients by cohort.

Summary of duration between start date of study drug and cut-off date, and follow-up times for PFS/OS/DOR, are defined as follows:

- Duration between start date of study drug and data cut-off date = (Cut-off date – Start date of study drug + 1) / 30.4375 (months).
- Follow-up time for PFS/OS = (Date of event or censoring – Start date of study drug + 1) / 30.4375 (months) regardless of censoring. Date of censoring is defined as the last adequate tumor assessment date for PFS or last contact date (when the patient is known as alive) for OS.
- Follow-up time for DOR = (Date of event or censoring – Start date of response + 1) / 30.4375 (months) regardless of censoring

Quartiles, minimum and maximum as well as the frequency count and percentage of patients in each of <1.5, 1.5-<3, 3-<6, 6-<9, 9-<12, ≥12 months will be reported for PFS, OS and DOR.

All summaries will be reported in months (see Section 4.4). The calculations for DOR and PFS will be based on BIRC assessment. Date of censoring is the same as defined for the DOR, PFS and OS analysis.

2.8.2 Safety

All safety analyses will be performed based on the Safety Set by cohort and also for all patients. Safety will also be presented combining the MET mutant cohorts and amplified cohorts as defined in Section 2.2.

Baseline

Baseline is the result of an investigation describing the "true" uninfluenced state of the patient. The last available assessment before or on the start date of study drug is defined as "baseline" value or "baseline" assessment. If an assessment is planned to be performed prior to the first dose of study drug in the protocol and the assessment is performed on the same day as the first administration of study drug, it will be assumed that it was performed prior to study drug administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. See Section 4.7.2 for further details on derivation of baseline for laboratory data and ECGs.

Patients who start treatment and discontinue from the study on the same day may have 2 different sets of data collected on study day 1, one being reported to the cycle 1 day 1 visit, the other reported to the end of treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

Grouping for the analyses

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

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study drug
- On-treatment period:
  - For discontinued patients, from day of first dose of study drug to 30 days after last dose of study drug
  - For ongoing patients, from day of first dose of study drug to the data cut-off date
- Post-treatment period: starting at day 31 after last dose of study drug

The safety summary tables will include only assessments collected no later than 30 days after study drug discontinuation and assessments prior to the data cut-off date for on-going patients, unless otherwise specified.

For select items, shift tables or change from baseline summaries generated for laboratory, ECG, vital signs and change score generation may use data from pre-treatment period for baseline calculations.

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

Adverse events (AEs)

AEs will be coded using MedDRA using the latest version available prior to clinical database lock and will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an AE, grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected on the fatal outcome from "Adverse event", "End of Treatment Phase completion", "End of post-treatment phase Completion" or "Death" eCRF pages.

All AE summaries will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum severity grades, except where otherwise noted. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event.

The following AE summaries will be produced:

- AEs regardless of study drug relationship
- AEs suspected to be study drug related
- On-treatment deaths, by primary system organ class and preferred term
- All deaths, by primary system organ class and preferred term
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related
- AEs leading to permanent discontinuation of study drug regardless of study drug relationship
- AEs leading to permanent discontinuation of study drug suspected to be study drug related
- AEs requiring dose adjustment and/or study drug interruption regardless of study drug relationship
- AEs requiring dose adjustment and/or study drug interruption suspected to be study drug related
- AEs requiring dose adjustment regardless of study drug relationship
- AEs requiring dose adjustment suspected to be study drug related
- AEs requiring study drug interruption regardless of study drug relationship
- AEs requiring study drug interruption suspected to be study drug related
- AEs requiring significant additional therapy regardless of study drug relationship
- AEs requiring significant additional therapy suspected to be study drug related
- Non-SAEs (AEs excluding SAEs) regardless of study drug relationship

In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

A listing will be provided to document any terms changed as a result of the re-mapping process to the latest MedDRA version available.

All AEs regardless of study drug relationship and all AEs suspected to be study drug related will be summarized by cohort and subgroup (as described in Section 2.2) using the safety set.

Exposure-adjusted overall incidence

The number and percentage of patients with any AEs along with the 95% confidence interval (95% CI) will be presented [Clopper and Pearson 1934]. In order to account for potential differences in exposure across groups, incidence rates of adverse events will be presented adjusted for Subject-Months exposure. [Sahai and Khurshid, 1993; Ulm 1990].

The exposure-adjusted overall incidence rate is defined as the number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in Subject-Months is counted up to the first qualifying event (or end of time at risk for patients without event). AEs missing start date for exposure-adjusted overall incidence calculation is handled as follows: Start date of study drug will be considered as the AE start date for any AE with missing start date.

Adverse events of special interest

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound INC280. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

All AESI definitions or AE grouping are specified in the electronic Case Retrieval Strategy (eCRS), in which they are identified by the flag "SP". Additional AESI may be reported if there are any updates to the eCRS at the time of the analyses.

Adverse events of special interest (AESIs) INC280 are:

- Hepatotoxicity
- Renal dysfunction
- ILD/Pneumonitis
- Central nervous system toxicity
- Pancreatitis
- Photosensitivity
- Teratogenicity
- Drug-drug interactions with strong CYP3A4 inducers
- QTc interval prolongation

This classification reflects the current version of the eCRS and might be updated based on review of accumulating data.

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

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

Analysis of time to first occurrence of any grade AESI will be applied as well as time to first occurrence of grade 3/4 AESI using the Kaplan-Meier method (see below the definitions). Duration of first occurrence of grade 3/4 AESI will also be summarized. These analyses will be performed for AESI regardless of study drug relationship and for AESI suspected to be study drug related.

For time to first occurrence, failure curves (ascending Kaplan-Meier curves) will be constructed in the combined MET mutant cohorts and all patients. Median together with 95% CI as well as 25th and 75th percentiles will be presented. In addition, the median time to occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics (median, min and max, 25th and 75th percentiles) will be presented. The probabilities at selected time points and the associate 95% CI will also be summarized.

Duration of first occurrence of grade 3/4 AESI will be presented for the subset of patients who experienced the event. Failure curves (ascending Kaplan-Meier curves) will be constructed in the combined MET mutant cohorts and all patients. Median together with 95% CI as well as 25th and 75th percentiles will be presented.

Duration of first occurrence of an event will be presented for the subset of patients of the safety set who experienced the event. A patient will be censored for time to resolution, if there is no resolution during the on-treatment period. The same censoring rules as described below for time to first occurrence apply.

Time to first occurrence

- Time to first occurrence of an event is defined as time from start of study treatment to the date of first occurrence of this event (or first event within an AE grouping), i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1.
- In the absence of an event during the on-treatment period, the censoring date applied will be the earliest of the following dates: death date, new anti-neoplastic antineoplastic therapy start date, end date of on-treatment, analysis cut-off date, and withdrawal of informed consent date. See Section 2.7.1 for the definition of new anti-neoplastic antineoplastic therapy.

Duration of first occurrence (i.e. Time to resolution of an event)

- Duration of first occurrence of an event is defined as time from onset to the date of resolution of the first event: (date of resolution of first event) – (date of onset of event) + 1.
- Resolution of the event means that outcome of the Grade 3/4 event is "recovered/resolved", "recovered/resolved with sequelae", or "recovering/resolving" (returning to grade ≤ 2). The same preferred term as the 1st event identified is used to determine the resolution. The resolution occurring after end of treatment + 30 days will be considered.
- The date of resolution of first Grade 3/4 event is derived as follows:
    - = End date of the first Grade 3/4 event *if the first event is resolved* (i.e. duration of AE). If multiple Grade 3/4 events with the same start date are reported, the latest end date will be considered (i.e. the longest duration of AE).
    - = Start date of the 1st Grade ≤ 2 event *if the first event is improved*. If multiple Grade 3/4 events with the same start date are reported, the latest start date of the

1st Grade ≤ 2 event will be considered (i.e. the longest duration of first occurrence).

- = Start date of the 1st Grade ≤ 2 event *if the first event is worsened and then improved*, and no Grade 3/4 AE with an outcome "resolved/recovered" reported later on. If multiple Grade 3/4 events with the same start date are reported, the latest start date of the 1st Grade ≤ 2 event will be considered (i.e. the longest duration of first occurrence).
- = End date of the Grade 3/4 event reported with outcome "recovered/resolved" *if the first event is worsened and then resolved* and Grade 3/4 AE with an outcome "resolved/recovered" reported.

With

- *Worsened: Event with a non-missing end date and outcome "not recovered/ not resolved"*
- *Improved: Event with a non-missing end date and outcome "recovering/not resolving". Event with a lower grade are expected to be reported*
- *Resolved: Event with a non-missing end date and outcome "recovered/ not resolved" or "resolved/resolved with sequelae"*

Section 4.7.4 provides further details on the definition of first occurrence and duration.

Deaths

Separate summaries for on-treatment and all deaths will be produced by cohort, primary system organ class and preferred term.

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

Laboratory data

For laboratory data assessments, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments collected no later than 30 days after study drug discontinuation. All laboratory assessments will be listed and those collected later than 30 days after study drug discontinuation will be flagged in the listings.

Laboratory data will be classified (by Novartis Oncology Statistical Programming) into CTC grades according to the NCI CTCAE v4.03. For all reports, CTC grade is always obtained on the converted measurement in SI unit. Grade 5 will not be used.The CTC grade 0 will be assigned as below in different scenarios:

- For lab parameters defined by criteria based on normal range only, a severity grade of 0 will be assigned when the value is within normal limits.
- For lab parameters whose grade is defined by criteria based on normal range and absolute values (e.g. platelet count decrease). A severity grade of 0 will be assigned when the value is within normal limits.

- For lab parameters whose grade is defined by criteria based on normal range and the change from baseline value, with no other associated clinical criteria such as concomitant medication (e.g. creatinine increased) the following will be applied. For the baseline grading and for the grading of post-baseline lab values with missing baseline grading, the grade will be derived using the criteria based only on the normal range as per CTCAE v4.03. A severity grade of 0 will be assigned when the post-baseline value is ≤ ULN (for hyper) or ≥ LLN (for hypo).

Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

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

- Shift tables using CTC grades to compare baseline to the worst post-baseline value for laboratory parameters with CTC grades
- Shift tables using low, normal, high (as well as low and high combined) classifications to compare baseline to the worst post-baseline value for laboratory parameters where CTC grades are not defined.
- New or worsened abnormalities for laboratory parameters based on CTC grade
- Trends of renal function parameters (creatinine, BUN) over time (baseline and selected on-treatment time-points, See Table 4-6) will be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following lab parameters will be summarized by cohort:

- Hematology: absolute lymphocytes, absolute neutrophils, hemoglobin (anemia), WBC, platelet counts, absolute basophils, absolute eosinophils, absolute monocytes, hematocrit
- Biochemistry: alkaline phosphatase (ALP), SGPT (ALT), SGOT (AST), total bilirubin, amylase, potassium, sodium, creatinine, glucose (hypo only), phosphate, albumin, calcium, magnesium, creatinine, direct bilirubin, blood urea nitrogen (BUN), GGT, lipase.
- For bi-directional parameters, both hyper and hypo summaries will be presented.

The following laboratory parameters will be presented in listings and will not be summarized:

- Urinalysis: macroscopic panel (dipstick) (bilirubin, blood, glucose, WBC, pH, protein, specific gravity), Urinalysis Microscopic panel (RBC, WBC, casts).
- Coagulation: INR, pro-thrombin time (PT) or Quick Test

The following listings will be produced for the laboratory data for all laboratory parameters where CTC grades are defined:

- Listing of patients with laboratory abnormalities of CTC grade 3 or 4
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

Liver function parameters of interest are total bilirubin (TBIL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values will be summarized by cohort in the following categories:

- ALT >3×ULN, >5×ULN, >8xULN, >10×ULN, >20×ULN
- AST >3×ULN, >5×ULN, >8×ULN, >10xULN, >20×ULN
- ALT or AST >3×ULN, >5xULN, >8×ULN, >10xULN, >20×ULN
- TBIL > 2xULN, >3×ULN

Combined and concurrent values post-baseline

- ALT or AST > 3xULN & TBIL> 2×ULN
- ALT or AST > 3×ULN & TBIL> 2×ULN & ALP ≥ 2×ULN
- ALT or AST > 3xULN & TBIL> 2×ULN & ALP < 2×ULN

Combined elevations values post-baseline (regardless of baseline levels)

- ALT or AST > 3xULN & TBIL> 2×ULN
- ALT or AST > 3×ULN & TBIL> 2×ULN & ALP ≥ 2×ULN
- ALT or AST > 3xULN & TBIL> 2×ULN & ALP < 2×ULN

Combined elevations values post-baseline by baseline levels

AST/ALT ≤ ULN at baseline

- ALT or AST > 3xULN & TBIL> 2×ULN
- ALT or AST > 3×ULN & TBIL> 2×ULN & ALP ≥ 2×ULN
- ALT or AST > 3xULN & TBIL> 2×ULN & ALP < 2×ULN

AST/ALT > UNL at baseline

- Elevated ALT or AST & TBIL (>2×Baseline and 2×ULN)
- Elevated ALT or AST & TBIL (>2×Baseline and 2×ULN) & ALP ≥ 2×ULN
- Elevated ALT or AST & TBIL (>2×Baseline and 2×ULN) & ALP <2×ULN

with Elevated AST or ALT defined as: >3×ULN if ≤ ULN at baseline, or (>3×Baseline or 8×ULN) if > ULN at baseline

In addition, a listing of all TBIL, ALT, AST and ALP values for patients with a post-baseline TBIL > 2xULN, ALT> 3xULN or AST > 3xULN will be provided.

The relationship between post-baseline increases in ALT/AST and total bilirubin will be shown using eDISH plot: peak values of Total bilirubin vs peak values of ALT/AST at any time during the course of treatment (not necessarily concurrent).

Analysis of time to first occurrence of grade 3/4 AST/ALT (whichever occurs first) will be done. Time to first occurrence of grade 3/4 AST/ALT and duration of the first occurrence of grade 3/4 AST/ALT will be summarized using Kaplan-Meier method. Patients with grade 3/4 AST/ALT at baseline will be excluded from the analysis. Median together with 95% CI as well as 25^{th} and 75^{th} percentiles will be presented. In addition, the median time to occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics

(median, min and max, 25th and 75th percentiles) will be presented. The probabilities at selected time points and the associate 95% CI will also be summarized.

Duration of first occurrence of grade 3/4 AST/ALT will be presented for the subset of patients who experienced the event. Median together with 95% CI as well as 25th and 75th percentiles will be presented.

ECGs

ECG data will be analyzed based on central laboratory reported results by cohort. The summaries will include all ECG assessments performed no later than 30 days after the last date of study drug. All ECG assessments will be listed, and those collected later than 30 days after study drug discontinuation will be flagged in the listing.

The number and percentage of patients with notable ECG values will be presented by cohort.

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

In addition the following analysis will be carried out;

- Descriptive statistical analysis (mean and two-sided 90% confidence interval) by time point of assessment for ΔQTcF (QTcF change from baseline).
- A graphical presentation of ECG mean change from baseline over time will be produced based on time windows.
- Shift table based on notable values to compare baseline to the worst post-baseline value for QT, QTcF and QTcB.
- Summary of newly occurring post-baseline qualitative ECG abnormalities.

Vital signs

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

Clinically notable elevated values are defined as:

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

Clinically notable below normal values are defined as:

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Body temperature: ≤ 35°C
- Weight: decrease from baseline of ≥ 10%
- Pulse rate: ≤ 50 bpm with decrease from baseline of ≥ 25%

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for pulse rate, diastolic BP and systolic BP.

Baseline values (Low/high) are defined as:

- Systolic BP: ≤ 90 mmHg ; Systolic BP: ≥ 180 mmHg
- Diastolic BP: ≥ 105 mmHg ; Diastolic BP: ≤ 50 mmHg
- Body temperature: ≤ 35°C ; Body temperature: ≥ 39.1°C
- Pulse rate: ≤ 50 bpm ; Pulse rate: ≥ 100 bpm

Patients with clinically notable vital sign abnormalities will be listed. All vital sign assessments will be listed by patient and vital sign parameter by cohort.

In the listings, clinically notable values will also be flagged.

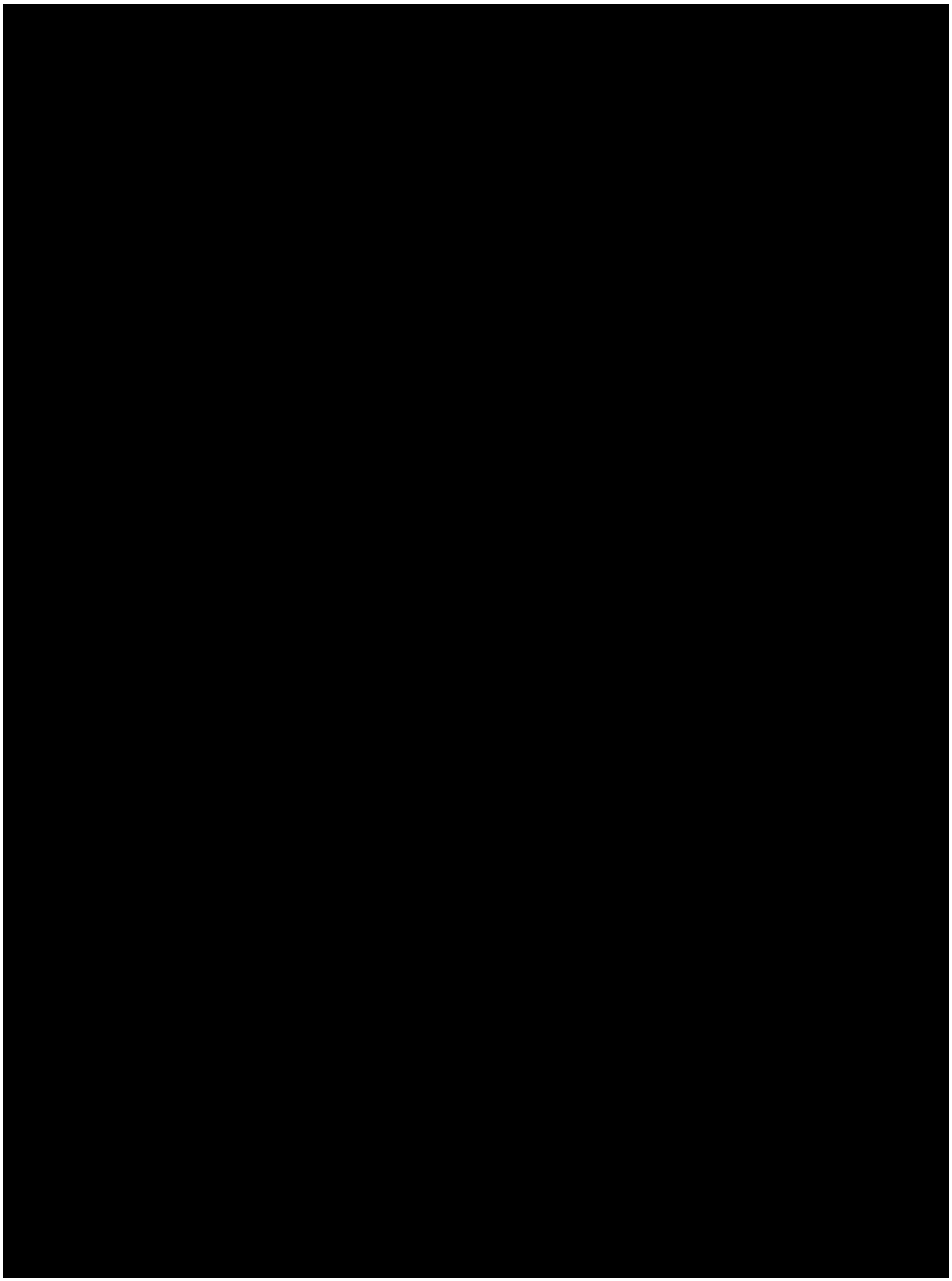
ECOG performance status

The ECOG performance status assessment allows patients to be classified as to their functional impairment, the definition of scores in relation to their performance status is provided in Table 2-2, ranging from 0 (most active) to 5 (dead):

Table 2-2 ECOG performance scale

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

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



[redacted]

2.8.4 Pharmacokinetics

Not applicable.

2.8.5 Pharmacogenetics/pharmacogenomics

Not applicable.

[redacted]

2.8.7 PK/PD

Not applicable.

2.9 Sample size calculation

Approximately 456 patients (69 patients per cohort in Cohorts 1a, 1b, 2, 3, 4 and 27 patients per each Cohort 5a, 5b, approximately 30 patients in Cohort 6 and approximately 27 patients in Cohort 7) will be enrolled in the study if none of the cohorts 1-4 is stopped for futility at the time of the interim analysis. The exact 95% CIs for various sample sizes and observed ORRs in each cohort 1-4 are shown in Table 2-4 and in Table 2-5 for cohorts 5a, 5b and 7.

Table 2-4 Exact Binomial 95 percent Confidence Intervals for Various Sample Sizes and Observed ORRs in Each Cohort

Sample size (N)	Number of responders	Observed ORR (%)	95% exact CI (%)	
65	23	35.4	23.9	48.2
66	24	36.4	24.9	49.1
67	24	35.8	24.5	48.5
68	24	35.3	24.1	47.8
69	**25**	**36.2**	**25.0**	**48.7**
70	25	35.7	24.6	48.1
71	25	35.2	24.2	47.5
72	26	36.1	25.1	48.3

Table 2-5 Exact Binomial 95 percent Confidence Intervals for Various Sample Sizes and Observed ORRs in each cohort 5a, 5b and 7

Sample size (N)	Number of responders	Observed ORR (%)	95% exact CI (%)	
25	14	56.0	34.9	75.6
26	15	58.0	36.9	76.6
27	**15**	**55.6**	**35.3**	**74.5**
28	16	57.1	37.2	75.5
29	16	55.2	35.7	73.6

The operating characteristics (with 69 patients per cohort in 1a, 1b, 2, 3 and 4) are shown in Table 2-6 and Table 2-7. The tables show probability of stopping at interim, probability for positive conclusion (i.e., not stopped at IA for futility and success criteria met at final analysis) and negative conclusion (i.e., not stopped at IA for futility but success criteria not met at final analysis) under different underlying true ORR. The operating characteristics (with 27 patients per cohort in 5a, 5b and 7) are shown in Table 2-8. The table shows the probability of meeting the success criteria under different underlying true ORR.

Cohort 1a, Cohort 1b, Cohort 2 and Cohort 4

The operating characteristics at this sample size have > 50% probability of stopping the trial for futility when the true ORR is < 25%. Also, when the true ORR is 35% then the probability of positive conclusion at the final analysis with 69 patients is ≥ 44%. If the true ORR is 45% or higher, the probability of positive conclusion at the final analysis with 69 patients is > 90%.

Table 2-6 Operating Characteristics for Cohort 1 (MET GCN ≥ 6) and Cohort 2 (MET GCN ≥ 4 and < 6)

True ORR (%)	Probability of a cohort to stop at IA* (%)	Probability for positive conclusion in final analysis for a cohort (%)	Probability for negative conclusion in final analysis for a cohort (i.e. not stop at IA* and success criterion not met at final analysis) (%)
10	99.50	0.00	0.50
20	81.82	0.12	18.06
25	59.97	2.34	37.68
30	36.48	15.01	48.51
35	18.21	44.00	37.79
40	7.40	75.38	17.22
45	2.42	93.11	4.47
50	0.63	98.73	0.64
*Assuming interim analysis at 28 evaluable patients			

Cohort 3 (MET GCN < 4)

The operating characteristics at this sample size have > 60% probability of stopping the trial for futility when the true ORR is < 25%. With 69 patients and 20 evaluable patients for interim analysis, when the true ORR is 10% then the probability of stopping for futility at the interim analysis is >90%. If the true ORR is 20%, the probability of stopping for futility at the interim analysis is >80% and the probability of positive conclusion at the final analysis is <1%.

Table 2-7 Operating Characteristics for Cohort 3 (MET GCN < 4)

True ORR (%)	Probability of a cohort to stop at IA* (%)	Probability of positive conclusion in final analysis for a cohort (%)	Probability of negative conclusion in final analysis for a cohort (i.e., not stop at IA* and success criterion not met at final analysis) (%)
10	98.87	0	1.13
20	80.42	0.11	19.47
25	61.72	2.17	36.12

True ORR (%)	Probability of a cohort to stop at IA* (%)	Probability of positive conclusion in final analysis for a cohort (%)	Probability of negative conclusion in final analysis for a cohort (i.e., not stop at IA* and success criterion not met at final analysis) (%)
30	41.64	13.98	44.39
35	24.54	41.41	34.05
40	12.56	71.99	15.45
45	5.53	90.46	4.01
50	2.07	97.36	0.57

*Assuming interim analysis at 20 evaluable patients

Cohort 5a, 5b and 7

The operating characteristics at this sample size of 27 have < 36% probability of the trial meeting the success criteria when the true ORR is ≤ 50%. If the true ORR is ≥ 60%, the probability of the trial meeting the success criteria is ≥ 75%.

Table 2-8 Operating Characteristics for Cohort 5a, 5b and 7

Sample size (N)	True ORR (%)	Probability (%) that ORR≥55% with lower 95% CI>35%
27	40	7.4
27	45	18.1
27	50	35.1
27	55	55.6
27	60	75.0
27	65	88.9

Cohort 6

In expansion Cohort 6, patients with either MET GCN ≥ 10 without MET mutations or MET mutations regardless of MET GCN will be enrolled. Based on the rarity of this patient population and considering recruitment within a reasonable timeframe, approximately 30 patients are expected to be enrolled in Cohort 6.

Data from Cohort 6 will help further characterize the safety and efficacy of INC280 in the pre-treated population (from Cohort 1a and Cohort 4).

2.10 Power for analysis of key secondary variables

Not applicable.

2.11 Interim analysis for futility

In Cohort 1, the interim analysis for futility will be performed separately for each of the two cohorts. Interim analyses for futility for each cohort are planned when at least 28 patients in each of Cohorts 1a, 1b, 2 and 4, and 20 patients in Cohort 3 have completed at least 6 cycles of treatment (18 weeks) or have discontinued treatment earlier. Due to the expected difference in enrollment rate for each cohort, the interim analysis for the different cohorts may occur at different times. For the interim analysis and the final analysis in Cohort 2 (MET GCN ≥ 4 and

< 6), the study targets to have at least 40% of patients with MET GCN ≥ 5 and < 6. No interim analysis is planned for Cohorts 5a, 5b and 6.

The decision to stop for futility for the respective cohort at interim will be based on the probability of success (POS). POS is the probability of a positive conclusion of the study if the study continued beyond interim, (i.e., till the final analysis), given the interim observed data (x) and success among n patients. Thus,

POS = Prob[Final observed ORR ≥ 35% | x,n]

Minimally informative Beta distribution prior (Neuenschwander 2008) with prior mean equal to 25% will be used, i.e., the prior distribution will be Beta (0.3333, 1) for the POS calculations at the interim analysis.

The respective cohort will be stopped for futility at the interim analysis if the respective POS < 10%.

Cohort 1a, Cohort 1b, Cohort 2 and Cohort 4

With 28 evaluable patients for interim analysis in each of the Cohorts 1a, 1b, 2 and 4, if ≤ 7 responses (POS =0.0543) are observed then the respective cohort will be stopped for futility. Further details of POS are provided in Table 2-9. For each of the Cohorts 1a, 1b, 2 and 4, if at the time that the 28th patient is enrolled a minimum of 8 responders have not yet been observed, accrual in the cohort may be temporarily suspended until either the minimum number of 8 responders are observed or results of the interim analysis allow that cohort to continue.

Table 2-9 Probability of Success at the Final Analysis Based on Various Number of Responders Observed at IA for Cohort 1a, Cohort 1b, Cohort 2 and Cohort 4

Responder at IA out of 28 evaluable patients at IA	Probability of Success
≤ 5	< 0.01
6	0.0164
7	0.0543
8	**0.1398**
9	0.2863
10	0.4794
11	0.6766
≥ 12	> 0.83

Table 2-10 Number of Responders for Various Number of Evaluable Patients at Interim Analyses by Required Probability of Success for Cohort 1a, Cohort 1b, Cohort 2 and Cohort 4

Number of Evaluable patients at IA	Responders at IA	Probability of Success
26	6	0.0368
26	7	0.1050
27	7	0.0765
27	8	0.1829
28	7	0.0543
28	**8**	**0.1398**

Number of Evaluable patients at IA	Responders at IA	Probability of Success
29	7	0.0377
29	**8**	**0.1044**
30	8	0.0760
30	**9**	**0.1792**
31	8	0.0540
31	**9**	**0.1369**
32	8	0.0373
32	**9**	**0.1020**
33	9	0.0740
33	**10**	**0.1739**
34	9	0.0523
34	**10**	**0.1323**
35	10	0.0980
35	**11**	**0.2152**

Cohort 3

With 20 evaluable patients for interim analysis in Cohort 3 if ≤ 5 responses (POS=0.0999) are observed then the cohort will be stopped for futility. All evaluable patients at the time of the data cut-off for the interim analysis will be used to obtain the futility boundary using the POS criteria. Further details of POS are provided in Table 2-11. If at the time that the 20th patient is enrolled a minimum of 6 responders have not yet been observed, accrual in the cohort may be temporarily suspended until either the minimum number of 6 responders are observed or results of the interim analysis allow the cohort to continue.

Table 2-11 Probability of Success at the Final Analysis Based on Various Number of Responders Observed at IA for Cohort 3 (MET GCN less than 4)

Responder at IA out of 20 evaluable patients at IA	Probability of Success
1	0.0001
2	0.0009
3	0.0066
4	0.0309
5	0.0999
6	**0.2379**
7	0.4382
8	0.6533

3 Changes to protocol specified analyses

Not applicable.

4 Additional details on implementation of statistical methodology

The sections below contain additional details on statistical methodology that will be included in Appendix 16.1.9 (Documentation of Statistical Methods) of the CSR as well as rules details on programing rules that will be followed to implement the analyses described in Section 2.

4.1 Data included in the analyses

This section provides additional details to those included in Section 2.1.

The primary analysis will be conducted when all treated patients in their respective cohort that is not stopped for futility have completed at least 6 cycles of treatment (18 weeks) or a patient has discontinued treatment earlier. Each analysis will include the data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date. For example, if the cut-off date is 30-Dec-2008, an AE starting on 30-Dec-2008 will be reported, whereas an adverse event starting on 31-Dec-2008 will not be reported.

4.2 Patient classification into analysis sets

This section provides additional details to those included in Section 2.2.

Patients are excluded from the analysis populations based on the protocol deviations entered in the database and/or on specific patient classification rules as shown in Table 4-1 below.

Table 4-1 Patient classification rules

Analysis Population	Additional patient classification rules leading to exclusion
Full Analysis Set	Patients who did not receive at least one dose of study drug
Safety Set	Patients who did not receive at least one dose of study drug.
Per-Protocol Set	Protocol deviations that will lead to removal of patients from Per Protocol Set (defined in Section 2.2)

4.3 Last contact date

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

Table 4-2 Last contact date data sources

Source data	Conditions
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.

Source data	Conditions
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor assessment date	Evaluation is marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the patient 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 is coming from 'Survival information' eCRF.

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

4.4 Time unit

For all derivations, a month will be calculated as (365.25 / 12) = 30.4375 days.

If duration is to be reported in years, duration in days will be divided by 365.25.

If duration is to be reported in months, duration in days will be divided by 30.4375.

If duration is to be reported in weeks, duration in days will be divided by 7.

4.5 Dose interruptions and dose changes

This section provides additional details to those included in Section 2.6.

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

An interruption is defined as a 0 mg dose taken on one or more days between two non-zero dosing periods. The last zero dose of INC280 followed by permanent discontinuation are not considered as dose interruption.

What follows defines how dose interruptions will be counted in the case of multiple dose interruptions.

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

actual dose on days 4-5 is 0 mg and dose interruption on day 4 is due to AE and dose interruption on day 5 is due to dosing error, then the total number of dose interruptions is 2).

- If an interruption occurs for more than one day due to the same reason, but the days are not consecutive, i.e. there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (*example: if the actual dose on days 1, 3 and 5, is 800 mg and actual dose on days 2 and 4 is 0mg, and dose interruptions on day 2 and 4 are both due to dosing error, the total number of dose interruptions is 2*).

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

Dose reductions are a subset of dose changes where the total daily dose is lower than the previous non-zero dose.

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

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0001	22/03/2017	25/03/2017	400	ONCE PER DAY	DOSING ERROR	**Y**	1st administration different from protocol planned dose (800 mg)
	26/03/2017	26/05/2017	800	2 TIMES PER DAY			

Case 2: If, due to a dosing error, a patient receives higher than protocol planned dose and moves down to the planned dose then this is not a dose reduction ([800 mg, 1000 mg, 800 mg] or [600 mg, 900 mg, 600 mg] ; However if the change is directly from a higher than planned dose down to a lower than protocol planned dose, then this is a dose reduction (e.g. In the sequence [800 mg, 1000 mg, 400 mg] or [600 mg, 900 mg, 400 mg], is a dose reduction).

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0002	22/03/2017	21/05/2017	800	2 TIMES PER DAY			
	22/05/2017	23/05/2017	0		ADVERSE EVENT		
	24/05/2017	01/08/2017	600	2 TIMES PER DAY	ADVERSE EVENT	Y	
	02/08/2017	02/08/2017	700	2 TIMES PER DAY	DOSING ERROR		
	03/08/2017	05/08/2017	800	2 TIMES PER DAY			
	06/08/2017	06/08/2017	**1000**	**2 TIMES PER DAY**	**DOSING ERROR**		
	07/08/2017	12/09/2017	**800**	**2 TIMES PER DAY**		**N**	moves down to the dose administered just before dosing error
0003	22/03/2017	21/05/2017	800	2 TIMES PER DAY			
	22/05/2017	23/05/2017	0		ADVERSE EVENT		

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
	24/05/2017	01/08/2017	600	2 TIMES PER DAY	ADVERSE EVENT	Y	
	02/08/2017	02/08/2017	700	2 TIMES PER DAY	DOSING ERROR		
	03/08/2017	05/08/2017	800	2 TIMES PER DAY			
	06/08/2017	06/08/2017	**1000**	**2 TIMES PER DAY**	**DOSING ERROR**		
	07/08/2017	12/09/2017	**600**	**2 TIMES PER DAY**		**Y**	moves down to a lower dose administered just before dosing error

Case 3: If due to interruption, a patient receives half of the dose during 1 day and followed by an interruption (due to the same reason) then this is not a dose reduction (for ex: 800 mg 2 times per day from 27-Dec-2016 to 14-Jan-2018, and 400 mg once per day on 15-Jan-2018 and then interruption 16-Jan-2018 to 22-Jan-2018). After interruption, dose reduction will be determined using the dose received on a day without interruption (for ex: 600 mg vs 800 mg ignoring 400 mg on 15-Jan given it is related to the interruption).

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0004	27/12/2017	14/01/2018	800	2 TIMES PER DAY			
	15/01/2018	15/01/2018	**400**	**ONCE PER DAY**	**ADVERSE EVENT**	**N**	½ dose for 1 day same reason than interruption Interruption started on 15-Jan
	16/01/2018	22/01/2018	0		**ADVERSE EVENT**		
	23/01/2018	07/02/2018	600	2 TIMES PER DAY	ADVERSE EVENT	**Y**	Dose reduction from 800 mg to 600 mg [400 mg on 15Jan ignored for reduction determination as part of the interruption]
	08/02/2018	19/02/2018	0		ADVERSE EVENT		
0005	25/04/2016	22/05/2016	800	2 TIMES PER DAY			
	23/05/2016	23/05/2016	400	ONCE PER DAY	ADVERSE EVENT	N	½ dose for 1 day same reason than interruption Interruption started on 23-May
	24/05/2016	25/05/2016	0		ADVERSE EVENT		
	26/05/2016	26/05/2016	400	ONCE PER DAY	ADVERSE EVENT	Y	Dose reduction from 800 mg to 400 mg [400 mg on 23May ignored for reduction determination as part of the interruption]
	27/05/2016	05/06/2016	800	2 TIMES PER DAY			
	06/06/2016	06/06/2016	400	ONCE PER DAY	DOSING ERROR	Y	

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
	07/06/2016	01/08/2016	800	2 TIMES PER DAY			
	02/08/2016	02/08/2016	400	**ONCE PER DAY**	**DOSING ERROR**	**Y**	½ dose for 1 day different reason than interruption
	03/08/2016	07/08/2016	0		**ADVERSE EVENT**		

Case 4: If due to permanent discontinuation, a patient receives half of the dose the last day of treatment then this is not a dose reduction (for ex: 800 mg 2 times per day from 30-May-2016 to 03-Oct-2016, and 400 mg once per day on 04-Oct-2016). This rule is applied for any dose levels (for ex: 600 mg 2 times per day from 15-Dec-2017 to 20-Dec-2017, and 300 mg once per day on 04-Oct-2016).

Patient ID	Start date	End date	Dose	Regimen	Reason	Permanently discontinuation	Reduction (derived)
0006	30/05/2016	03/10/2016	800	2 TIMES PER DAY			
	04/10/2016	04/10/2016	400	ONCE PER DAY	ADVERSE EVENT	Y	N

4.6 Efficacy endpoints

For further details on efficacy endpoints, see Section 14 (Appendix II) of the protocol. For the evaluation of tumor-response related endpoints, response is assessed by investigator and BIRC according to RECIST 1.1.

Response and progression evaluation will be performed according to the Novartis RECIST 1.1 guidelines, included in Section 14 (Appendix II) of the CINC280A2201 protocol.

The text below gives more detailed instructions and rules needed for programming of the analyses described in Sections 2.7 and 2.8.1.

4.6.1 Implementation of RECIST guidelines

Disease progression

PD should only be assigned if it is confirmed by an objective assessment method as per RECIST 1.1 (e.g. radiologic scan, histology for bronchoscopy, photos for skin lesions). If a new lesion is detected using an objective assessment method other than radiologic scan, it should be entered on the 'New lesion' RECIST eCRF with appropriate method (or method='Other').

In particular, discontinuation due to disease progression or death due to progressive disease, without supporting objective evidence (as defined above), will not be considered as PD in the determination of BOR, the derivation of any efficacy endpoint or efficacy analysis.

Change in imaging modality

Per RECIST 1.1, a change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-

versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT and vice versa while keeping same contrast use (e.g. switching from spiral CT with contrast to CT with contrast) is not considered a change in imaging modality. A change in methodology will result by default in a UNK (unknown) overall lesion response assessment. However, a response assessment other than the Novartis calculated UNK response may be accepted from the investigator or BIRC if a definitive response assessment can be justified based on the available information. Potential discrepancies between the modality used and overall lesion response reported by the investigator (e.g. change in modality but investigator assessment of response is different from UNK) will be queried during the data validation process.

Determination of missing adequate tumor assessments

For the computation of ORR, patients without any radiological assessment after the start date of study drug will be counted as failure.

Partial or complete responses reported prior to any additional anticancer therapy will be considered for ORR computation irrespective of the number of missed assessments before response. In this section, the 'missing adequate assessment' is defined as assessment not done or assessment with overall lesion response equal to UNK. For the sake of simplicity, the 'missing adequate assessment' will also be referred as 'missing assessment'.

As detailed in Section 14 (Appendix II) of the CINC280A2201 protocol, the PFS censoring and event date options depend on the presence and the number of missing tumor assessments. *For example, an event occurring after two or more missing assessments is censored in the analysis of PFS at the last adequate tumor assessment before the event date*.

An exact rule to determine whether there is none, one or two missing assessments is therefore needed. This rule will be based on the distance between the last adequate tumor assessment date and the event date.

If the distance is larger than threshold D_1 or D_2 then the analysis will assume one or two missing assessments, respectively. The threshold D_1 will be defined as the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. Similarly, the threshold D_2 is defined as two times the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. In this study, the protocol defined schedule of tumor assessment is every 6 weeks and each assessment is expected to be performed at the scheduled time point plus or minus 1 week, i.e. the window is 2 weeks, then any distance larger than $D_1 = 6+2 = 8$ weeks means one missing assessment and any distance larger than $D_2 = (2*6) + 2 = 14$ weeks means two missing assessments.

The same definition of D_2 will be used to determine the PFS censoring reason.

Possible censoring reasons for PFS are:

1: Ongoing without event

2: Lost to follow-up

3: Withdrew consent

4: Adequate assessment no longer available

5: New cancer therapy added

6: Event after >=2 missing tumor assessments

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

- If patient is considered to have a PFS event then PFS censoring reason is set to missing.
- Else if patient has had no baseline assessment then PFS censoring reason = 4.
- Else if patient has a PFS event after two or more missing assessments [If (PFS Event date ≤ Censoring date and (PFS Event date - Date of last adequate tumor assessment (LATA) ≥ D2)] then PFS censoring reason =6:
- Else if patient has no PFS event, and patient is censored at a date after two or more missing assessments ((Censoring date - Date of LATA) ≥ D2) then PFS censoring reason = 4
- Else if censoring date equals the start date of further anti-neoplastic therapy then PFS censoring reason = 5
- Else if censoring date equals date of discontinuation due to consent withdrawal then PFS censoring reason = 3
- Else if censoring date equals date of discontinuation due to loss to follow-up then PFS censoring reason = 2
- Else if the censoring date equal the analysis cut-off date and the time between LATA and the cut-off is greater than D2 days then PFS censoring reason = 4
- Else if the censoring date equal the analysis cut-off date and the time between LATA and the cut-off is less than or equal to D2 days then PFS censoring reason = 1

Where censoring date = minimum(analysis cut-off date, start date of further anti-neoplastic therapy, date of discontinuation due to consent withdrawal, date of discontinuation due to loss to follow-up).

Non-measurable disease at baseline

As specified in Section 14 (Appendix II) of the CINC280A2201 protocol, the RECIST 1.1 criteria imply that only patients with measurable disease at baseline should be included in the study. If a patient without measurable disease is enrolled, the intent-to-treat (ITT) principle requires including these patients in the analyses. Hence, analyses will be based on FAS including patients with either measurable or non-measurable disease. Therefore, a rule needs to be specified on how to handle these cases.

As specified in Table 3-1 of Section 14 (Appendix II) of the CINC280A2201 protocol, overall lesion response can be derived for patients without measurable disease at baseline as follows (Table 4-3).

Table 4-3 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination.

Missing baseline tumor assessment

As specified in Section 14 (Appendix II) of the protocol, since the timing of PD cannot be determined for patients with missing baseline tumor assessment, these patients are censored in the PFS analysis at the start date of treatment. This rule, however, only applies to the 'PD component' of the PFS or DOR assessment.

Patients without baseline tumor assessment who die within D_2 distance from start date of treatment will be counted as having an event in the primary analysis of PFS. All deaths will be counted in the OS analysis regardless of presence or absence of the baseline tumor assessment.

Construction of waterfall graphs

The waterfall graphs will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the sum of the measured diameter of all target lesions based on the on-treatment assessments occurring prior to the first PD for each patient with measureable disease at baseline. The proportions of patients with various degrees of tumor shrinkage or growth can then represent a useful efficacy metric.

However, caution needs to be paid to the assessments, where an occurrence of a new lesion or worsening in non-target lesions (resulting in PD as an overall lesion response at given assessment) contradicts the measurements obtained on target lesions. These assessments will not be displayed as bars in the graph. If such a "contradicting" assessment represents the only post-baseline assessment for a patient, then the patient will be represented by a special symbol (e.g. *) in the waterfall graph.

The assessments with unknown target response and also assessments with unknown overall response will be excluded. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph needs to be shown and this number will be used as a denominator when calculating the percentages of patients with tumor shrinkage and tumor growth. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

Patient who have discontinued will be represented by a special symbol in the waterfall graph.

All possible assessment scenarios are described in Table 4-4.

Table 4-4 Inclusion/exclusion of assessments used in waterfall graph

Criteria for inclusion/exclusion			Possible source of contradictions	
Target response	**Overall lesion response**	**Include in waterfall**	**Non-target response**	**New lesion?**
CR/PR/SD	PD	Yes but as * only	PD	any
CR/PR/SD	PD	Yes but as * only	Any	Yes
UNK	UNK or PD	No	Any	any
CR/PR/SD	UNK	No	UNK	No
CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
PD	PD	Yes as a bar	Any	any

The following algorithm will be used to construct the graph:

1. Select "valid" post-baseline assessments to be included, i.e. for each patient and each assessment repeat the following four steps:

1.1. Check the target lesion response and overall lesion response at each assessment. If at least one of them is UNK then exclude the whole assessment. Otherwise, go to step 1.2.

1.2. Check the overall lesion response. If PD, then go to step 1.3. Otherwise, go to step 1.4

1.3. Check target response. If PD, then go to step 1.4. Otherwise flag the assessment ✶.

1.4. Calculate the % change from baseline in target lesions.

2. For each patient, go through all valid assessments identified in step 1 and find the assessment with best % change from baseline in target lesions. The "best" means best for the patient, i.e. the largest shrinkage or if a patient only has assessments with tumor growth take the assessment where the growth is minimal. (*Example 1*: Patient 1 has the following % changes from baseline at assessments 1, 2, 3, 4 and 5, respectively: -10%; -25%; -13%; -4% and +6%. His/her best % change is then -25%. *Example 2*: Patient 2 has the following % changes from baseline at assessments 1, 2 and 3, respectively: +5%; +18% and +35%. His/her best % change is then +5%.
3. Construct the waterfall graph displaying the best % change from baseline for each patient. Patients having only ✶ flagged assessment(s) will be displayed separately.

Both investigator assessment and BIRC will be used in the construction of waterfall plot.

The recommended way of the display from left to right is:

1. Bars under the horizontal axis representing tumor shrinkage
2. Bars above the horizontal axis representing tumor growth
3. "Zero" bars with ✶ symbol representing patients with contradiction

4.6.2 Sources for overall lesion response

The tumor endpoints derivation is based on the sequence of overall lesion responses at each assessment/time point. However, the overall lesion response at a given assessment/time point will be provided from different sources as illustrated in Table 4-5.

Table 4-5 Sources for overall lesion response

Source 1	BIRC (Blinded Independent review committee) reported overall lesion response
Source 2	Investigator (local radiology) reported overall lesion response

In this study, Source 1 will be used for the primary endpoint derivation and other secondary endpoint calculations based on BIRC assessment (ORR, DOR, DCR, TTR and PFS). Source 2 will be used to calculate ORR, DOR, DCR, TTR and PFS by Investigator assessment.

4.6.3 Kaplan-Meier estimates

To analyze time to event variables (DOR, TTR, OS and PFS) an estimate of the survival function will be constructed using ***Kaplan-Meier (product-limit) method*** as implemented in PROC LIFETEST with METHOD=KM option (see example below). The median time to event and estimated event rates at different time points will be estimated, along with associated 95% two-sided CIs derived based on the complementary log-log transformation. This will be conducted via the SAS procedure LIFETEST. The TIME statement will include a variable with survival times (*survtime* in the example below) and a (right) censoring variable (*censor* in the example below) with a value of 1, representing censoring:

```
PROC LIFETEST data = dataset
   METHOD = KM
   CONFTYPE=LOGLOG;
TIME survtime*censor(1);
RUN;
/* survtime represents variable containing event/censor times;
censor represents censoring variable (1 = censored, 0 = event); */
```

Kaplan-Meier survival and failure function estimates from this procedure will be used to construct the Kaplan-Meier figures.

Median survival will be obtained along with 2-sided 95% CIs calculated from PROC LIFETEST output using the method of Brookmeyer & Crowley, 1982.

Kaplan-Meier estimates with 2-sided 95% CIs at specific time points will be summarized. The time points can be expressed in weeks or in months depending on the time-to-event variable. The CIs will be constructed using Greenwood's formula [Collet, 1994, p.23] for the standard error of the Kaplan-Meier estimate.

The Kaplan-Meier graphs will be constructed using SAS software.

4.6.4 Confidence interval and p-value for response rate

ORR 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 & Pearson, 1934).

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided Pearson-Clopper CI and exact one-sided p-value for the hypothesis test of the *null proportion* (0.25). These estimates are obtained as follows:

```
proc freq data = dataset;
      table binary event /
            binomial(
                  p = null proportion
                  level = "Yes")
            alpha = two-sided alpha level;
      exact binomial;
```

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used as specified above except changing **level**="No". From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

$$LCL_{LEVEL="Yes"}\ (\%) = 100\% - UCL_{LEVEL="No"}\ (\%)$$

$$UCL_{LEVEL="Yes"}\ (\%) = 100\% - LCL_{LEVEL="No"}\ (\%)$$

4.6.5 Baseline

Baseline is the result of an investigation describing the "true" uninfluenced state of the patient. The last available assessment before or on the start date of study drug is defined as "baseline" value or "baseline" assessment.

[redacted]

4.7 Safety evaluations

The text below gives more detailed instructions and rules needed for programming of the analyses described in Section 2.8.2.

4.7.1 Multiple assessments within post-baseline visits

For all analyses regarding abnormal assessments or analyses based on worst or best post-baseline value (laboratory, ECGs, vital signs, ECOG performance status), all post-baseline values will be included (scheduled, unscheduled, repeat). All unscheduled and repeat measurements will be included in listings.

Laboratory Data

For laboratory data, assessments can be collected from both local and central laboratory on the same date. For shift tables using CTC grades to compare baseline to the worst post-baseline value, the assessment with worst post-baseline value is used for analyses irrespective of the source. For LFT summaries, where concurrent measurements are used in the calculation of number and percentage of patients with worst post-baseline values, the assessment with worst post-baseline value is used (since worst values are based on the largest ratio of lab value to its ULN for each patient) although the worst values for the different parameters may be coming from different laboratories.

ECGs

For all patients, 3 ECGs are targeted to be measured at the protocol-defined (nominal) time-points. If a patient has more than one measurement at a nominal scheduled time point, the average of all available measurements associated with the nominal time point will be used for the analyses. For unscheduled visits, measurements taken within 15 min interval will also be averaged and used for analysis.

4.7.2 Baseline

As defined in Section 2.8.2, the last available assessment before or on the date of start of study drug is defined as “baseline” value or “baseline” assessment.

Laboratory data

If both central and local laboratory assessments were performed on the same date and corresponding to the baseline assessment date, then the central laboratory assessment will be used for the calculation of baseline.

If labs with duplicate laboratory measurements taken at the last assessment date on or before the start date of study treatment from the same sources (both from local or central), then the rule described below will be applied for the calculation of baseline.

- For gradable labs, the value of lower CTCAE grade will be considered as the baseline value. If several records have the same absolute grade, but in different directions, 2 baselines should be created, the record with grade below 0 should be the baseline of the 'Hypo' parameter, and the other record should be the baseline for the 'Hyper' parameters.
- For non-gradable labs:
  - If both within normal range: take average value
  - If one within normal range and the other outside: take the one within normal range
  - If both outside normal range: take the one closest to the normal range

ECGs

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

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

4.7.3 Laboratory Parameters

This section provides further detail on the analysis of laboratory parameters that will be listed and summarized as described in Section 2.8.2.

Hematology

Hematologic tests include: Hemoglobin, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute)

The following rules will be applied to derive the WBC differential counts when only percentages are available (this is mainly for neutrophils and lymphocytes, because CTC grading is based on the absolute counts).

The method to convert the value is straightforward: for each patient, the original lab value (%) is divided by 100 and multiplied by WBC count e.g. for neutrophils (NEU):

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

In order to derive the corresponding absolute normal range, the rule to be applied depends on the availability of the % range and the absolute range for the differential:

- If % absolute range NOT missing (% range is or isn't missing), then use the absolute range provided by the site
- If % range NOT missing and absolute range missing, then the % normal limits (i.e LLN and ULN) are divided by 100 and multiplied by the corresponding normal limits of WBC count, e.g. for neutrophils NEU):

  LLN for NEU count = (LLN for WBC count)* (LLN for NEU%value /100)

  ULN for NEU count = (ULN for WBC count)*(ULN for NEU%value/100)

Biochemistry

The following calculation will be applied for corrected calcium in SI unit (if not available in the Lab database):

Corrected calcium (mmol/L)=measured total Ca (mmol/L)+0.02 (40-serum albumin[g/L]), where 40 represents the average albumin level in g/L.

Time windows will be defined for trends of labs over time.

Table 4-6 Time windows for Labs

Time Window	Planned Visit Timing	Time Window Definition
Baseline	On or before Study Day 1	≤ Study Day 1
Cycle 1 Day 15 (Week 3)	Study Day 15	Study Days 2 – 18
Cycle 2 Day 1 (Week 4)	Study Day 22	Study Days 19 – 32
Cycle 3 Day 1 (Week 7)	Study Day 43	Study Days 33 – 53
Cycle 4 Day 1 (Week 10)	Study Day 64	Study Days 54 – 74
Cycle 5 Day 1 (Week 13)	Study Day 85	Study Days 75 – 95
Cycle 6 Day 1 (Week 16)	Study Day 106	Study Days 96 – 116
Cycle 7 Day 1 (Week 19)	Study Day 127	Study Days 117 – 137
Every 6 weeks thereafter	Scheduled visit day (+ 21 days from previous cycle)	Scheduled visit day ± 10 days centered around the planned assessment

Study Day 1 = the first day of dosing

4.7.4 Time to first occurrence of event and duration

This section provides additional details to those included in Section 2.8.2. For each case, the start date and end date for the duration of the 1st occurrence are in bold.

Case 1a: First event resolved with a single event - Outcome = recovered/resolved

Patient ID	Preferred term	Start date	End date	Grade	Outcome
0001	INCREASED LIPASE	**2016-05-31**	**2016-06-02**	3	RECOVERED/RESOLVED

Case 1b: First event resolved with multiple events with the same start date - Outcome = recovered/ resolved

Patient ID	Preferred term	Start date	End date	Grade	Outcome
0002	INCREASED AMYLASE	2018-10-01	2018-10-29	3	RECOVERED/RESOLVED
	INCREASED LIPASE	**2018-10-01**	**2018-11-20**	3	RECOVERED/RESOLVED

Case 2a: The first event improved with a single event - Outcome = recovering/resolving

Patient ID	Preferred term	Start date	End date	Grade	Outcome
0003	ILD	**2017-08-30**	2017-09-20	3	RECOVERING/RESOLVING
	ILD	**2017-09-21**	2017-10-06	2	NOT RECOVERED/NOT RESOLVED
	ILD	2017-10-07		3	NOT RECOVERED/NOT RESOLVED

Case 2b: The first event improved with multiple events with the same start date - Outcome =recovering/resolving

Patient ID	Preferred term	Start date	End date	Grade	Outcome
0004	**AST INCREASED**	**2017-11-30**	2017-12-06	3	RECOVERING/RESOLVING
	HYPOALBUMINEMIA	2017-11-30	2017-12-06	2	RECOVERING/RESOLVING
	ALT INCREASED	**2017-11-30**	2017-12-13	3	RECOVERING/RESOLVING
	GGT INCREASED	2017-11-30	2018-01-12	2	RECOVERED/RESOLVED
	ALP INCREASED	2017-12-06	2017-12-13	1	RECOVERED/RESOLVED
	AST INCREASED	2017-12-06	2017-12-13	2	RECOVERING/RESOLVING
	ALT INCREASED	**2017-12-13**	2017-12-20	2	RECOVERING/RESOLVING
	AST INCREASED	2017-12-13	2017-12-20	1	RECOVERED/RESOLVED
	ALT INCREASED	2017-12-20	2018-01-12	1	NOT RECOVERED/NOT RESOLVED
	AST INCREASED	2018-01-12	2018-01-22	3	RECOVERING/RESOLVING
	ALT INCREASED	2018-01-12	2018-01-25	4	RECOVERING/RESOLVING

Case 2c: The first event improved (Gr 4, Gr 3 and Gr <3) - Outcome =recovering/resolving

Patient ID	Preferred term	Start date	End date	Grade	Outcome
0005	**HEPATIC DYSFUNCTION**	**2017-01-06**	2017-01-11	4	RECOVERING/RESOLVING
	HEPATIC DYSFUNCTION	2017-01-12	2017-01-18	3	RECOVERING/RESOLVING
	HEPATIC DYSFUNCTION	**2017-01-19**	2017-02-06	1	RECOVERED/RESOLVED

Case 3a: The first event worsened and then improved (Gr 3, Gr 4 and Gr <3) - Outcome =not recovered/not resolved and then recovering/resolving

Patient ID	Preferred term	Start date	End date	Grade	Outcome
0006	AMYLASE INCREASE	2017-07-13	2017-07-18	2	RECOVERING/RESOLVING
	AMYLASE INCREASE	2017-07-19	2017-08-29	1	NOT RECOVERED/NOT RESOLVED
	AMYLASE INCREASE	**2017-08-30**	2017-09-05	3	NOT RECOVERED/NOT RESOLVED
	AMYLASE INCREASE	2017-09-06	2017-09-10	4	RECOVERING/RESOLVING
	AMYLASE INCREASE	2017-09-11	2017-09-21	3	RECOVERING/RESOLVING
	AMYLASE INCREASE	**2017-09-22**		1	NOT RECOVERED/NOT RESOLVED

Case 3b: The first event worsened with multiple events and then improved (Gr 3, Gr 4 and Gr <3) - Outcome =not recovered/not resolved and then recovering/resolving

Patient ID	Preferred term	Start date	End date	Grade	Outcome
0007	AMYLASE INCREASED	**2017-09-12**	2017-10-05	3	NOT RECOVERED/NOT RESOLVED
	AMYLASE INCREASED	2017-10-06	2017-10-20	3	RECOVERING/RESOLVING
	LIPASE INCREASED	2017-10-06	2017-10-20	1	RECOVERED/RESOLVED
	AMYLASE INCREASED	**2017-10-20**	2017-10-26	1	NOT RECOVERED/NOT RESOLVED
	LIPASE INCREASED	2017-10-26	2017-11-03	3	RECOVERED/RESOLVED
	AMYLASE INCREASED	2017-10-27	2017-11-20	3	RECOVERING/RESOLVING
	AMYLASE INCREASED	2017-11-20	2017-12-11	2	RECOVERED/RESOLVED
	AMYLASE INCREASED	2017-12-11		1	NOT RECOVERED/NOT RESOLVED

Case 4: The first event worsened and then resolved - Outcome =not recovered/not resolved and then recovered/resolved

Patient ID	Preferred term	Start date	End date	Grade	Outcome
0008	HEPATOTOXICITY	**2015-11-17**	2015-11-22	3	NOT RECOVERED/NOT RESOLVED
	HEPATOTOXICITY	2015-11-23	2015-12-02	4	RECOVERING/RESOLVING

	HEPATOXICITY	2015-12-03	**2016-01-19**	3	RECOVERED/RESOLVED WITH SEQUELAE
	GGT INCREASED	2016-01-05		2	NOT RECOVERED/NOT RESOLVED

4.7.5 Handling of AEs missing grade

- Missing grade will be included under 'All grades' column for AE tables displaying 'Grade 3/4' and 'All grades'.
- Missing grade will be counted twice for AE tables by maximum grade (displaying Total, Grade 1–4 and Missing).

4.8 Imputation rules

4.8.1 Study drug

The following rules 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 end of treatment (EOT) page and no death date, the patient is considered as on-going.

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

Scenario 2

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

- Case 1: The dose end date is completely missing and the EOT completion date is complete, then this latter date should be used.
- Case 2: Only year (YYYY) of the dose end date is available and YYYY < the year of EOT date, then use 31DECYYYY
- Case 3: Only year (YYYY) of the dose end date is available and YYYY = the year of EOT date, then use EOT date
- Case 4: Both year (YYYY) and month (MMM) are available for dose end date and YYYY = the year of EOT date and MMM < the month of EOT date, then use last day of the Month (MMM)
- Case 5: Both year (YYYY) and month (MMM) are available for dose end date and YYYY = the year of EOT date and MMM = the month of EOT date, then use EOT date

All other cases should be considered as a data issue and the 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

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

4.8.2 AE date imputation

The following missing dates will not be imputed

- Missing AE start dates
- AE start dates missing the year
- Partial/missing AE end dates

AE with uncertain relationship will be considered as treatment-emergent AE.

For other types of missing dates, the rules specified in Tables 4-7 to Table 4-10 will be used.

Table 4-7 AE/treatment date abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 4-8 describes the possible combinations and their associated imputations. The upper text indicates the imputation (NC, A, B, C etc.) and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 4-8 Imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The legend to the above table is shown in Table 4-9.

Table 4-9 Imputation algorithm legend

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation calculation	
NC / Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY

Relationship	
(D)	01JULYYYY
(E)	01JANYYYY

A few examples are shown in Table 4-10.

Table 4-10 Example scenarios

Partial AE start date	Treatment start date	Relationship with TRTSTD	Imputation Calculation	Imputed Date
12MMMYYYY	20OCT2001	Uncertain	NC	<blank>
DDMMM2000	20OCT2001	Before	(D)	01JUL2000
DDMMM2002	20OCT2001	After	(E)	01JAN2002
DDMMM2001	20OCT2001	Uncertain	(B)	21OCT2001
DDSEP2001	20OCT2001	Before	(C)	15SEP2001
DDOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
DDNOV2001	20OCT2001	After	(A)	01NOV2001

4.8.3 Concomitant medication date imputation

The imputation of the start date of concomitant medication will follow the same conventions as for AE dates. Partial concomitant medication end dates will not be imputed.

4.8.3.1 Prior therapies date imputation

Start date

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that for scenario (B) it will be replaced with "start date of study drug −1".

End date

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

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

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date. If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Incomplete date of progression –Prior antineoplastic therapy-medication

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

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

4.8.3.2 Post therapies date imputation

Start date

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

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

End date

No imputation.

4.8.4 Other imputations

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

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

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

Incomplete assessment dates for tumor assessment

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

Incomplete or missing death date

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

- If only day is missing, then impute 15th day of the month and year of death.
- If both day and month are missing, then impute 01JUL of the year of death.

Exposure-adjusted overall incidence

- Start date of study treatment will be considered as the AE start date for any AE with missing start date for exposure-adjusted overall incidence calculation.

[redacted]

5 Reference:

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