NOVARTIS

Clinical Development

EGF816, INC280, Nivolumab

CEGF816X2201C / NCT02323126

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

Statisical Analysis Plan for CSR

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Document type: Amended SAP Version

Document status: Final

Release date: 17-Mar-2021

Number of pages: 29

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
30-Aug-2016	Prior to DB lock	Creation of final version	N/A - First version	NA
xx-Nov-2020	After LPLV and Prior to DB lock	To align with the latest protocol amendment 8 (dated on 12-Mar-2020)	• Updated statistical analysis and PK software versions • Updated the primary/final analysis timing • Added precise definition of "actually received" treatment • Added definitions of PK analysis sets • Updated the definition of dose intensity • Added sub-group definitions in Group 2 • [redacted] • Removed the Bayesian analysis of PFS rate at 3 months • [redacted]	• Section 2.1 • Section 2.1 • Section 2.2 • Section 2.2 • Section 2.5.1.1 • Section 2.2.1 • Section 2.2.1 • Section 2.7 • Section 2.10.5

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BCS	Biopharmaceutics Classification System
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
CI	Confidence Interval
Cmax	Maximum plasma concentration after a single dose
CR	Complete Response
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DDS	Dose Determining Set
DLT	Dose-Limiting Toxicity
DOR	Duration Of Response
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
EGF	Epidermal growth factor
EGFR	Epidermal Growth Factor Receptor; also known as ErbB1
EOT	End of Treatment
HGF	Hepatocyte Growth Factor
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MTD	Maximum Tolerated Dose
NCA	Non-Compartmental Analysis
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics or Progressive disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings

Tmax	Peak plasma concentration
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CEGF816X2201C that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the Tables, Figures, Listings (TFL) shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document.

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

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

1.1 Study design

This is a phase II, multi-center, open-label study of patients with advanced NSCLC.

Patients will be allocated based on their EGFR status to one of the two groups:

- Group 1: EGFR-T790M NSCLC. As of December 17, 2015, enrollment to Group 1 has been halted.
- Group 2: EGFR wild-type (wt) NSCLC. For the purpose of this protocol, EGFR wt is defined as negative for exon 19 deletions and for the L858R mutation in EGFR at a minimum; however, if more extensive EGFR mutation testing has been performed, the tumor must not harbor any known activating EGFR mutations in Exons 18-21 in order to be considered EGFR wt. Patients in Group 2 will be subdivided into two sub-groups:
  - Sub-group A : high cMet
  - Sub-group B: low cMet.

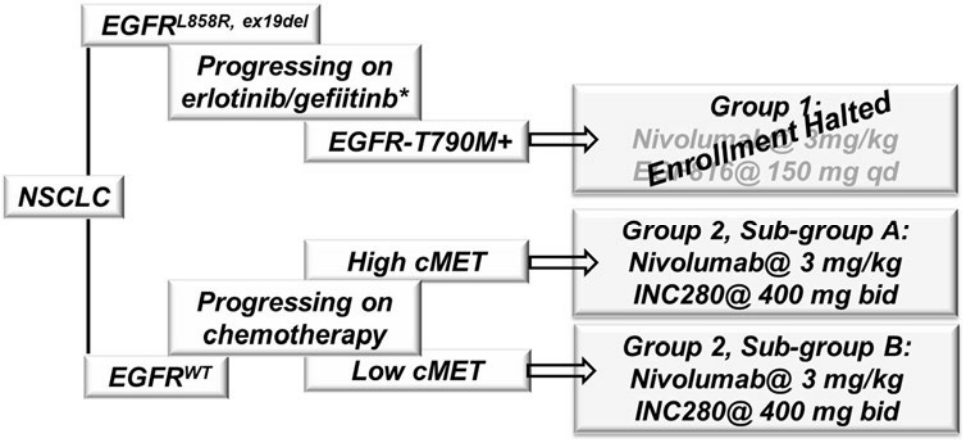
Based on group allocation, patients will be treated as follows:

- Group 1: EGF816+nivolumab. As of January 28, 2016, nivolumab was required to be discontinued from all ongoing patients in Group 1. Ongoing patients who re-consent to remain on study will be treated with EGF816 as a single agent.
- Group 2: INC280+nivolumab

A cycle will be defined as 28 days.

See Figure 1-1 for an overview of the study design

Figure 1-1 Study design



1.2 Study objectives and endpoints

Objectives and related endpoints are described respectively in Table 1-1 below:

Table 1-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To estimate the clinical activity of Nivolumab in combination with EGF816 or INC280	6 month PFS rate using RECIST version1.1 (6mo PFS rate=6 cycles=168 days)	Refer to 2.6.1
Secondary		
To evaluate the preliminary antitumor activity of EGF816 and Nivolumab and of INC280 and Nivolumab	ORR, DCR, other PFS measures, OS	Refert to 2.7
To characterize the safety and tolerability of EGF816 and Nivolumab or of INC280 and Nivolumab	Safety, incidence and severity of AEs, including changes in hematology and chemistry values, vital signs and ECGs Tolerability: Dose interruptions, reductions, and dose intensity	Refer to 2.8
To evaluate PK of EGF816, INC280 and Nivolumab in the combination setting	PK parameters of Nivolumab,EGF816 and INC280 such as Cmax, AUC and Cmin	Refer to 2.9
[redacted]		

Objective	Endpoint	Analysis
[redacted]		

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis personnel and/or designated CRO(s) using SAS version 9.4, and for Bayesian modeling, R version 3.6.1 or later. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 8.0 or later.

The study data will be analyzed and reported in a final CSR that includes all outputs planned within the TFL shells document.

Data from participating centers in this study protocol will be combined, so that an adequate number of patients will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic (PK) and pharmacodynamics (PD) measurements. Quantitative data will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) and categorical data will be summarized using contingency tables (frequencies and percentages).

Both pre and post intra-patient dose escalation data will be listed and summarized together under the one dose level/treatment group.

Data from patients in safety monitoring cohorts treated at doses different from the respective selected dose will be analyzed as separate groups for safety and BOR.

Sub-group A and sub-group B in Group 2 will be considered as separate treatment groups. Including Group 1 there will be total 3 treatment groups for all analyses. For analyses of safety and pharmacokinetics, additional information with sub-group A and sub-group B in Group 2 pooled will also be presented.

2.1.1 General definitions

Study drug and study treatment

Study drug refers to the individual compound, i.e., EGF816, INC280, and Nivolumab. Study treatment refers to any combination of study drugs, i.e.

- Group 1: EGF816+Nivolumab
- Group 2: INC280+Nivolumab

Study day

The study day for all assessments/events will be calculated using the start date of study treatment as reference. For assessments/events occurring on or after the start date of study treatment, study day will be calculated as:

Study day (days) = Event date – Start date of study treatment + 1

Therefore, the first day of study treatment is study day 1.

For all assessment/events occurring prior to the start of the study treatment, study day will be negative and will be calculated as:

Study day (days) = Event date – Start date of study treatment

Study day will be displayed in the data listings.

On-treatment assessment/event

An on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the start date of study treatment until the last date of study treatment + 100 days inclusive.

Baseline

Baseline is the last available and valid assessment performed or value measured within 28 days before the first dose, i.e. first administration of study treatment. Baseline can be on a day before or on the same day as first dose if a pre-dose assessment/value is available (e.g., ECG, PK samples, [redacted]).

If time is recorded for the first dose and for a specific assessment performed on the day of first dose, this assessment will be considered as baseline only if it is actually performed before the first dose, as checked using both times.

If time is not recorded, a specific assessment performed on the day of first dose will be considered as baseline if, according to protocol, it should be performed before the first dose.

Patients with no data on a particular parameter before the first dose will have a missing baseline for that parameter.

For pregnancy test, baseline will be within 72 hours before first dose.

Computation of baseline for ECG, [redacted] other endpoints are described in each specific section.

2.2 Analysis sets

The number (%) of patients in each of the defined analysis set will be summarized using the FAS.

Full analysis set

The Full Analysis Set (FAS) comprises all patients who have received at least one dose of INC280, EGF816 or Nivolumab. Patients will be analyzed according to the planned treatment they have been assigned to. Unless otherwise specified, the FAS will be used for all listings of raw data.

Safety set

The Safety Set includes all patients who received at least one dose of INC280, EGF816 or Nivolumab and have at least one valid post-baseline safety assessment. Please note that the statement that a patient had no AEs (on the AE eCRF page) constitutes a safety assessment.

Patients will be analyzed according to the study treatment (regimen) they actually received, where treatment actually received is defined as:

- The treatment assigned if it was received at least once, or
- If the assigned treatment was never received, then the first treatment received when starting therapy with study treatment will be used for classification

The safety set will be the primary population for all safety related endpoints.

Per-Protocol set

All major protocol deviations leading to exclusion from the PPS are listed below:

- Patients without written informed consent prior to any screening procedures
- Patients without presence of at least one measurable lesion according to RECIST v.1.1.
- Patients who have been treated with prior PD-1 and PD-L1 agents
- **Group 1 patients**
  - without EGFR T790M NSCLC (adenocarcinoma);
  - or without documented progression of disease according to RECIST v1.1 following primary standard of care (e.g. erlotinib, gefitinib);
  - or have received more than one prior line of EGFR TKI therapy.
- **Group 2 patients**
  - without EGFR wild-type NSCLC;
  - or without documented progression of disease according to RECIST v1.1 following primary standard of care (e.g. platinum doublet);
  - or had previous treatment with a cMet inhibitor or HGF-targeting therapy.

Patients will be classified according to treatment received.

The PPS will be used in the sensitivity analysis of the primary endpoint. If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

Pharmacokinetic Analysis Set (PAS)

Each of the EGF816 and INC280 PAS includes two sets, the EGF816/INC280 full pharmacokinetic analysis set (EGF/INC-FPAS) which will be used for non-compartmental analysis (NCA) and EGF816/INC280 pharmacokinetic analysis set (EGF/INC-PAS).

The EGF816/INC-PAS includes all patients who have provided at least one evaluable EGF816/INC280 PK concentration. For an EGF816/INC280 PK concentration to be evaluable, a patient must:

- Have taken at least one planned dose of EGF816/INC280 prior to sampling
- for INC280 PK samples taken on or after Cycle 1 Day 15, the patient took study drug according to the originally assigned dose for at least 3 consecutive days without interruption or dose modification prior to the PK sampling day (ensuring steady state is reached)
- for EGF816 take the same dose of EGF816 for at least 5 consecutive days prior to sampling on or after cycle 1 day 15
- For pre-dose samples, do not vomit within 4 hours after the dosing of EGF816/INC280 prior to sampling
- For post-dose samples, do not vomit within 4 hours after the dosing of EGF816/INC280
- For pre-dose sample of INC280, have the sample collected before the next dose administration and 9-15 hours after the last dose administration.
- For pre-dose sample of EGF816, have the sample collected 20 to 28 hours after the last dose administration and before the next dose administration.

The EGF/INC-FPAS includes all EGF/INC-PAS patients who have provided an EGF816/INC280 evaluable PK profile on cycle 1 day 15 (only applicable to patients with extensive PK sampling in the safety monitoring cohort). An EGF816/INC280 PK profile is considered evaluable if all of the following conditions are satisfied:

- Patient has received planned doses
- Patient has provided at least one valid primary PK parameter (AUClast, AUCtau, Cmax, Tmax)
-

The NIVO-PAS includes all patients who have provided at least one evaluable Nivolumab PK concentration. For a Nivolumab PK concentration to be evaluable, a patient must:

- Have received one of the planned doses (complete infusion) of Nivolumab prior to sampling
- For pre-dose samples, have the sample collected before the next dose administration

2.2.1 Subgroup of interest

The following two subgroups in Group 2 will be considered.

- Group 2A (cMet high): if any one of the following criteria is satisfied:
    - IHC score = 3+ in at least 50% of tumor cells (regardless of gene copy number (GCN))
    - IHC score = 2+ in at least 50% of tumor cells and GCN>=5
    - cMet exon 14 activating mutation positive
- Group 2B (cMet low): if negative or unknown for cMet exon 14 activating mutation AND any one of the following criteria is satisfied
    - IHC score = 2+ in at least 50% of tumor cells and GCN < 5
    - IHC score = 2+ in less than 50% of tumor cells (regardless of GCN)
    - IHC score = 0 or 1+ (regardless of GCN)

2.3 Patient disposition, demographics and other baseline characteristics

Unless noted otherwise, summaries and listings described in this section will be based on the FAS.

2.3.1 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. The followings will be tabulated:

- Number (%) of patients who are still on-treatment (based on non-completion of the 'End of Treatment' page),
- Number (%) of patients who discontinued treatment (based on completion of the 'End of Treatment' page with discontinuation date and reason entered),
- Primary reasons for study treatment discontinuation (based on discontinuation reason entered in the 'End of Treatment' page),
- Number (%) of patients who discontinued from study (based on completion of the 'End of Post Treatment Phase Disposition' page with discontinuation date and reason entered),
- Primary reasons for study evaluation completion (based on discontinuation reason entered in the 'End of Post Treatment Phase Disposition' page).

2.3.2 Demographics and other baseline characteristics

Demographic data including age, sex, race, ethnicity, height, baseline weight and ECOG performance status will be listed and summarized. In addition, child bearing potential and pregnancy test results will be listed, and age (18-<65, 65-<85, ≥85 years) and weight (<55, 55-75, ≥75 kg) categories summarized. For patients from Germany, HIV test results will be listed by treatment group.

2.3.3 Medical history

Medical history and current medical conditions will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting. Medical history and current (ongoing) medical conditions, including cancer-related conditions and symptoms will be listed.

2.3.4 Prior antineoplastic therapy

Prior anti-neoplastic therapy will be summarized and listed for medication, radiotherapy and surgery by treatment group.

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

Prior anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD). The following summary tables will be presented:

- Summary table of number and percentage of patients who received any prior anti-neoplastic medications, number of regimens, therapy type (e.g. chemotherapy, hormonal therapy, etc.) at last medication, setting (e.g. adjuvant, metastatic, etc.) at last medication, best response at last medication, time (days) from end of last treatment to start of study treatment.
- Summary table of ATC class and preferred term.

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

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

2.3.5 Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include primary site of cancer, details of tumor histology/cytology, histological grade, stage at time of study entry, time from initial diagnosis of primary site to start of study treatment, time since most recent recurrence/relapse or progression to start of study treatment, and time from initial diagnosis of primary site to first recurrence/relapse or progression.

2.4 Protocol deviations

The FAS will be used for the protocol deviation summary tables and listings. The number (%) of patients with any CSR-reportable protocol deviation will be tabulated by the deviation category (entry criteria not satisfied; wrong treatment or incorrect dose; developed withdrawal criteria, but not withdrawn; took an excluded concomitant medication; others). The full list of protocol deviations are documented in the Study Specification Document (SSD).

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

Unless otherwise stated, the Safety set will be used for all medication data summaries and listings.

2.5.1 Study treatment

2.5.1.1 Treatment exposure

Date of first/last administration of study treatment

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

Last date of exposure to study drug

For EGF816 and INC280 the last date of exposure to study drug is the last date of study drug.

For Nivolumab the last date of exposure to study drug is defined as follows.

- Last day of exposure = last day of administration + 13 days.

Last date of exposure to study treatment

Last date of exposure to study treatment = max (last date of exposure to any component of the study treatment).

Duration of study drug exposure

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

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

Duration of study treatment exposure

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

The exposure duration may include periods of temporary interruption. If a patient is still on treatment at the time of data cut-off, the end date of treatment will be replaced by the data cut-off date and the above respective algorithm will be used.

Actual cumulative dose (mg): sum of all doses of study drug taken by a patient.

Planned cumulative dose (mg): sum of all doses of study drug planned to be have been taken during the study treatment period by a patient.

Percentage of days dosed: 100 × number of actual doses taken ⁄ number of doses scheduled per protocol during treatment period.

Percentage of days at planned dose: 100 × number of doses at planned dose ⁄ number of doses scheduled per protocol during treatment period

Actual dose intensity (ADI):

- For EGF816 and INC280 (unit: mg/day): Actual cumulative dose (mg) / duration of exposure (days).
- For Nivolumab (unit: mg/kg biweekly): [Actual cumulative dose (mg/kg) / duration of exposure (days)]*14 days

Planned dose intensity (PDI), fixed for all patients:

- For EGF816 and INC280 (unit: mg/day): planned daily dose (i.e., 150 mg/day for EGF816 and 800 mg/day for INC280)
- For Nivolumab (unit: dose unit/cycle): planned dose per cycle (i.e., 3mg/kg biweekly)

Relative dose intensity (%): 100*ADI/PDI.

The duration of exposure to study treatment and study drug (including categories: <6, 6-<12, 12-<18, 18-<24, 24-<48, 48-<72, >=72 weeks) will be summarized. In addition, the cumulative dose, percentage of days dosed, percentage of days the planned/intended dose was received, DI, and RDI (including categories: <=0.5, 0.5<-<=0.75, 0.75<-<=0.9, 0.9<-<=1.1, >1.1) will be summarized for each study drug. The number (%) of patients who have dose reductions and interruptions (and/or delays), and the corresponding reasons, will be provided for each study drug. The number of dose reductions and interruptions (and/or delays) per patient and the duration of dose reductions/interruptions/delays (days) will be summarized for each study drug.

All doses of the study treatment along with reasons for any dose change will be listed.

Dose delay/interruption: Actual dose equal to zero where the planned dose is not zero, between the first and last non-zero doses, following a non-zero actual dose (if not the first dose).

Dose reduction: A non-zero actual dose that is less than the immediate previous non-zero actual dose (if not the first dose) and below the treatment received (see safety set) dose. No dose reduction is allowed for Nivolumab.

Intra-patient dose escalation: Dose change flag checked with reason “as per protocol”, and actual dose that is greater than any previous actual dose.

2.5.2 Concomitant and post therapies

2.5.2.1 Concomitant therapy

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Any concomitant therapies starting prior to or after the start of study treatment will be listed.

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 2.8.1 Adverse events). No imputation will be performed for concomitant medication end dates.

2.5.2.2 Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed.

2.5.3 Compliance

Compliance to the study treatment within each treatment group will be assessed by the number of dose reductions, number of dose interruptions and percent of days received planned dose for both study drugs separately in summary tables by treatment group for the safety set.

2.6 Analysis of the primary objective

The primary objective is to estimate the clinical activity of Nivolumab in combination with EGF816 or INC280.

2.6.1 Primary endpoint

The primary efficacy variable is PFS rate assessed at 6 months (more precisely after 6 cycles = 168 days) following either Nivolumab and EGF816 treatment or Nivolumab and INC280 treatment. CT/MRI assessments will be used for efficacy assessments of anti-tumor activity on study. PFS will be defined as per RECIST v1.1.

2.6.2 Statistical hypothesis, model, and method of analysis

For each treatment group a Bayesian design will be used. PFS will be modeled using a Weibull distribution (details are described in protocol Appendix 3). Assuming a weakly informative prior distribution for the PFS rate at 6 months, the distribution will be updated with all available data from patients treated at the confirmed dose in the FAS. The PFS rate at 6 months will be estimated from the posterior distribution. Inferential summaries (e.g., mean, median, standard deviation, 95% credible intervals, and interval probabilities) based on the posterior distribution will also be presented.

Group 1: Nivolumab and EGF816

For PFS rate at 6 months the indifference point is set at 70% and the inferential intervals are given below:

- [0, 55%) unacceptable anti-tumor activity
- [55%, 70%) limited anti-tumor activity
- [70%, 85%) moderate anti-tumor activity
- [85%, 100%] strong anti-tumor activity

If the posterior mean PFS rate at 6 months is equal to or greater than 70% and the posterior risk of being in the unacceptable anti-tumor activity interval [0, 55%) is lower than 5%, then preliminary anti-tumor activity of the study treatment will be declared. Posterior summaries for the 4 inferential intervals above will also be assessed.

Group 2: Nivolumab and INC280

Sub-group A: EGFR wild-type high cMet

For PFS rate at 6 months the indifference point is set at 50% and the inferential intervals are given below:

- [0, 35%) unacceptable anti-tumor activity
- [35%, 50%) limited anti-tumor activity
- [50%, 65%) moderate anti-tumor activity
- [65%, 100%] strong anti-tumor activity

If the posterior mean PFS rate at 6 months is equal to or greater than 50% and the posterior risk of being in the unacceptable anti-tumor activity interval [0, 35%) is lower than 5%, then preliminary anti-tumor activity of the study treatment will be declared. Posterior summaries for the 4 inferential intervals above will also be assessed.

Sub-group B: EGFR wild-type low cMet

For PFS rate at 6 months the indifference point is set at 40% and the inferential intervals are given below:

- [0, 25%) unacceptable anti-tumor activity
- [25%, 40%) limited anti-tumor activity
- [40%, 55%) moderate anti-tumor activity
- [55%, 100%] strong anti-tumor activity

If the posterior mean PFS rate at 6 months is equal to or greater than 40% and the posterior risk of being in the unacceptable anti-tumor activity interval [0, 25%) is lower than 5%, then preliminary anti-tumor activity of the study treatment will be declared. Posterior summaries for the 4 inferential intervals above will also be assessed.

2.6.3 Handling of missing values/censoring/discontinuations

The PFS time of patients who have not died or progressed at time of the primary analysis will be censored at the last adequate tumor assessment. For patients who initiate a new antineoplastic therapy without experiencing disease progression under study treatment, their PFS time will be censored at time of initiating the new antineoplastic therapy.

2.6.4 Supportive analysis

For each group the primary analysis of PFS rate at 6 months will be repeated using PPS, if PPS is different from FAS. In addition, the PFS rate at 6 months and the corresponding 95% confidence interval will be presented using Kaplan-Meier estimate.

Additional supportive [redacted] analyses will be conducted to support the primary objective if appropriate.

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objective is to evaluate the preliminary antitumor activity of EGF816 and Nivolumab and of INC280 and Nivolumab.

2.7.1 Secondary endpoints

The secondary efficacy endpoints include ORR, DCR, PFS, PFS rate at 3 months, and OS at 1 year. CT/MRI assessments will be used for all efficacy assessments of anti-tumor activity on study. BOR, ORR, DCR, PFS, and OS will be defined as per RECIST v1.1.

Secondary efficacy endpoints will be listed and summarized by treatment group. Median PFS and PFS rate at 3 months with the corresponding 95% confidence interval will be estimated using the Kaplan-Meier method. The Kaplan-Meier estimate of PFS will also be plotted. OS at 1 year with 95% confidence interval will be estimated using the Kaplan-Meier method.

2.7.2 Statistical hypothesis, model, and method of analysis

Waterfall plot to depict anti-tumor activity

Waterfall plot will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of all target lesions for each patient. Only patients with measurable disease at baseline will be included in the waterfall plots. Patients without any valid assessments at baseline or post-baseline will be excluded from the waterfall plot.

Overall response summary

A summary table of investigator assessment will be presented with count and percentage of each BOR category (CR, PR, SD, PD, Unknown), point estimate and the 95% confidence interval (CI) based on the exact binomial distribution for ORR and DCR. A listing will be presented with overall responses at all assessment timepoints, with percentage change from nadir or baseline, and BOR per patient.

PFS and OS

Median PFS and PFS rate at 3 months with the corresponding 95% confidence interval will be estimated using the Kaplan-Meier method. The Kaplan-Meier estimate of PFS will also be plotted.

For PFS and OS, Kaplan-Meier plot by treatment group will be produced. A summary table by treatment group with estimated median (in months), 25^{th} and 75^{th} percentiles with correspoinding 95% CIs as well as estimated probability at 3, 6, 12, 18 and 24 months with corresponding 95% CIs will be presented.

Individual overall response, time to progression and death, and time to onset and duration of overall response will be listed.

2.7.3 Handling of missing values/censoring/discontinuations

- ORR: If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be ‘Unknown’. If no valid post-baseline tumor assessments are available, the BOR must be “Unknown” unless progression is reported. Patients with unknown or missing BOR will be counted as failures.
- DOR: A patient who has not progressed or died at the date of the analysis or when he/she receives any further anticancer therapy in the absence of disease progression will be

censored at the time of the last adequate tumor evaluation before the earlier of the cut-off date or the anticancer therapy date.

- PFS: A patient who has not progressed or died at the date of the analysis or when he/she receives any further anticancer therapy in the absence of disease progression will be censored at the time of the last adequate tumor evaluation before the earlier of the cut-off date or the anticancer therapy date. By default, if disease progression or death is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression or death is documented after two or more missing tumor evaluations, the PFS time of these patients will be censored at the date of the last adequate tumor evaluation without PD.

2.8 Safety analyses

The assessment of safety is based on the type and frequency of Adverse Events (AEs) as well as on the number of laboratory values that fall outside of pre-determined ranges (Common Toxicity Criteria for Adverse Events (CTCAE) grading limits or normal ranges as appropriate). Other safety data include electrocardiogram and vital signs.

The Safety set will be used for summaries and listings of safety data with the exception of dose limiting toxicities (DLTs) for which the DDS will be used.

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

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication,
2. On-treatment period: from day of first dose of study medication to 100 days after last dose of study medication,
3. Post-treatment period: starting at Day 101 after last dose of study medication.

The safety summary tables will include assessments collected no later than 100 days after study treatment discontinuation.

2.8.1 Adverse events (AEs)

AEs will be coded and graded using the latest version of MedDRA and CTCAE, respectively, available at the time of reporting. 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. Death information will be collected on the "End of Treatment" or "Survival Information" eCRF pages.

The following AE summaries will be produced:

- AEs regardless of study drug relationship (including CTC grade 3/4)
- AEs suspected to be study drug related (including CTC grade 3/4)
- AEs regardless of study drug relationship leading to discontinuation of study drug
- AEs suspected to be study drug related leading to discontinuation of study drug
- AEs regardless of study drug relationship requiring dose adjustment or study drug interruption
- AEs which are not SAEs regardless of study drug relationship

- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related

A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. A patient with multiple occurrences of an AE is counted only once in the AE category (e.g. system organ class, preferred term).

A missing AE start date will be imputed using the following logic matrix described in Table 2-1.

Table 2-1 Imputation rules for a partially missing AE start date

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	No imputation	No imputation	No imputation	No imputation
AEY < TRTY	(D)	(C)	(C)	(C)
AEY = TRTY	(B)	(C)	(B)	(A)
AEY > TRTY	(E)	(A)	(A)	(A)

AEM: Month AE started; AEY: Year AE started
TRTM: Month treatment started; TRTY: Year treatment started

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

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

	AE start date relationship	Imputation
(A)	After treatment start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(B)	Uncertain	TRTSTD+1
(C)	Before treatment start	15MONYYYY
(D)	Before treatment start	01JULYYYY
(E)	After treatment start	01JANYYYY

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

No imputation will be performed for AE end dates.

2.8.2 Deaths

All deaths occurred in the study will be listed with principal cause reported/preferred term and following summaries will be produced:

- On-treatment deaths with cause of death by preferred term
- All deaths with cause of death by primary system organ class and preferred term

2.8.3 Laboratory data

Laboratory data will be converted into SI units and classified (by Novartis statistical programming) into CTC grades according to CTCAE. Grade 5 will not be used.

For cases when the CTC grade definition includes change from baseline criteria (e.g., Creatinine, Ejection fraction, Fibrinogen, Hemoglobin, INR): When a lab value is of grade X based on threshold/ranges, but grade X+1 when considering change from baseline, the final Grade is set to X+1. For other cases, a Grade 0 CTC grade will be set when laboratory value is:

- Within LLN and ULN and grading in both direction,
- Below ULN and grading in hyper direction,
- Above LLN and grading in hypo direction.

Laboratory data for which a CTC grading does not exist will be classified into low, normal, or high based on local laboratory normal ranges as applicable.

The following summaries will be produced for hematology and biochemistry parameters:

- For parameters with CTC grades: Shifts from baseline to the worst post-baseline CTC grade,
- For parameters with no CTC grades defined: Shifts from baseline to the worst post-baseline using low/normal/high classifications,

The following listings will be produced:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges

Table 2-3 and Table 2-4 list all laboratory parameters that will be summarized.

Table 2-3 Laboratory parameters for which CTCAE grades are defined

Hematology and coagulation		Biochemistry	
White Blood Cells (WBC)	↑↓	Creatinine	↑
Hemoglobin	↓	Sodium	↑↓
Platelet counts	↓	Calcium	↑↓
Absolute Neutrophils	↓	Magnesium	↑↓
Absolute Lymphocytes	↑↓	Albumin	↓
INR	↑	AST (SGOT)	↑
		ALT (SGPT)	↑
		Chloride	↓
		Total Bilirubin	↑
		Glucose*	↑↓

↑ Indicates that CTC grade increases as the parameter increases.
↓ Indicates that CTC grade increases as the parameter decreases.
* Separate by fasting status if applicable (fasting or non-fasting)

Table 2-4 Laboratory parameters (without CTCAE grades) for which lab reference ranges are defined

Hematology and coagulation	Biochemistry
Prothrombin time (PT)	Blood urea nitrogen (BUN)
	Urea
	Total protein

2.8.4 Vital signs, weight and physical examinations

Vital sign parameters collected are systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), body temperature (°C), and weight (kg). Vital sign values considered notably abnormal are defined in Table 2-5.

Table 2-5 Criteria for notable vital sign values

Vital sign	Criteria for clinically notable vital sign values
Systolic blood pressure [mmHg]	≥180 mmHg/≤90 mmHg with increase/decrease from baseline of ≥20 mmHg
Diastolic blood pressure [mmHg]	≥105 mmHg/≤50 mmHg with increase/decrease from baseline of ≥15 mmHg
Pulse rate [bpm]	≥100 bpm/≤50 bpm with increase/decrease from baseline of >25%
Body temperature [°C]	≥ 39.1
Weight [kg]	≥10% decrease/increase from baseline

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.

Patients with any clinically notable vital sign value will be listed.

2.8.5 Electrocardiograms

Baseline for ECG analysis is defined as the average of all available ECG measurements associated with the baseline assessment. Scheduled study day 1 pre-dose ECGs will be considered to have been obtained prior to study drug administration if dosing time is missing.

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

The following summaries will be provided for each applicable ECG parameter:

- For each ECG interval (QTcF, QT, QRS, PR, HR), descriptive statistics at baseline, at worst post-baseline and change from baseline to worst post-baseline value for each parameter,
- For each QT interval (QT, QTcF), shift tables based on notable QT interval categories (≤450, >450 - ≤480, >480 - ≤500, >500 ms) at baseline to the worst post-baseline value observed**,**
- Number (%) of patients having notable ECG values according to Table 2-6.

Table 2-6 Criteria for notable ECG values

ECG parameter	Criteria for notable ECG values
QT, QTcF (ms)	Increase from baseline >30 ms to ≤60 ms, >60 ms
HR (bpm)	Increase from baseline >25% and value >100 bpm Decrease from baseline >25% and value <50 bpm
PR (ms)	Increase from baseline >25% and value >200 ms New PR >200 ms
QRS (ms)	Increase from baseline >25% and value >120 ms New QRS >120 ms

Patients with any notable change from baseline for each QT/QTc interval will be listed.

2.8.6 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of dose interruptions and dose reductions by treatment group. Reasons for dose interruption and dose reductions will be listed by patient and treatment group and summarized by treatment group in Phase I part and by Group in Phase II part. Cumulative dose, dose intensity and relative dose intensity of study treatment will be also be used to assess tolerability.

2.9 Pharmacokinetic data

PK concentration analyses and PK concentration summary statistics will be performed based on the INC-PAS, EGF-PAS and Nivo-PAS. Patient data may be removed on an individual basis. Only PK blood samples with the date and time and for which the last prior dose date and time are adequately recorded will be included in the calculation of PK parameters.

Concentration values below the lower limit of quantitation (LLOQ) will be displayed in listings as zero with a flag and handled as zero in the calculations for mean, CV for mean, standard deviation, minimum, median, maximum, but handled as missing for the calculation of the geometric means and their CV. Zero concentrations will not be included in the geometric mean calculation.

Sub-group A and sub-group B in Group 2 will be considered as separate treatment groups. In addition, results with sub-group A and sub-group B in Group 2 pooled will also be presented.

INC280, EGF816 and Nivolumab concentration data will be listed and summarized by time point, patient and treatment group. Descriptive statistics will include arithmetic and geometric mean, median, standard deviation, coefficient of variation (CV), geometric CV, minimum and maximum. Individual concentration-time profile as well as mean concentration-time profile will be plotted.

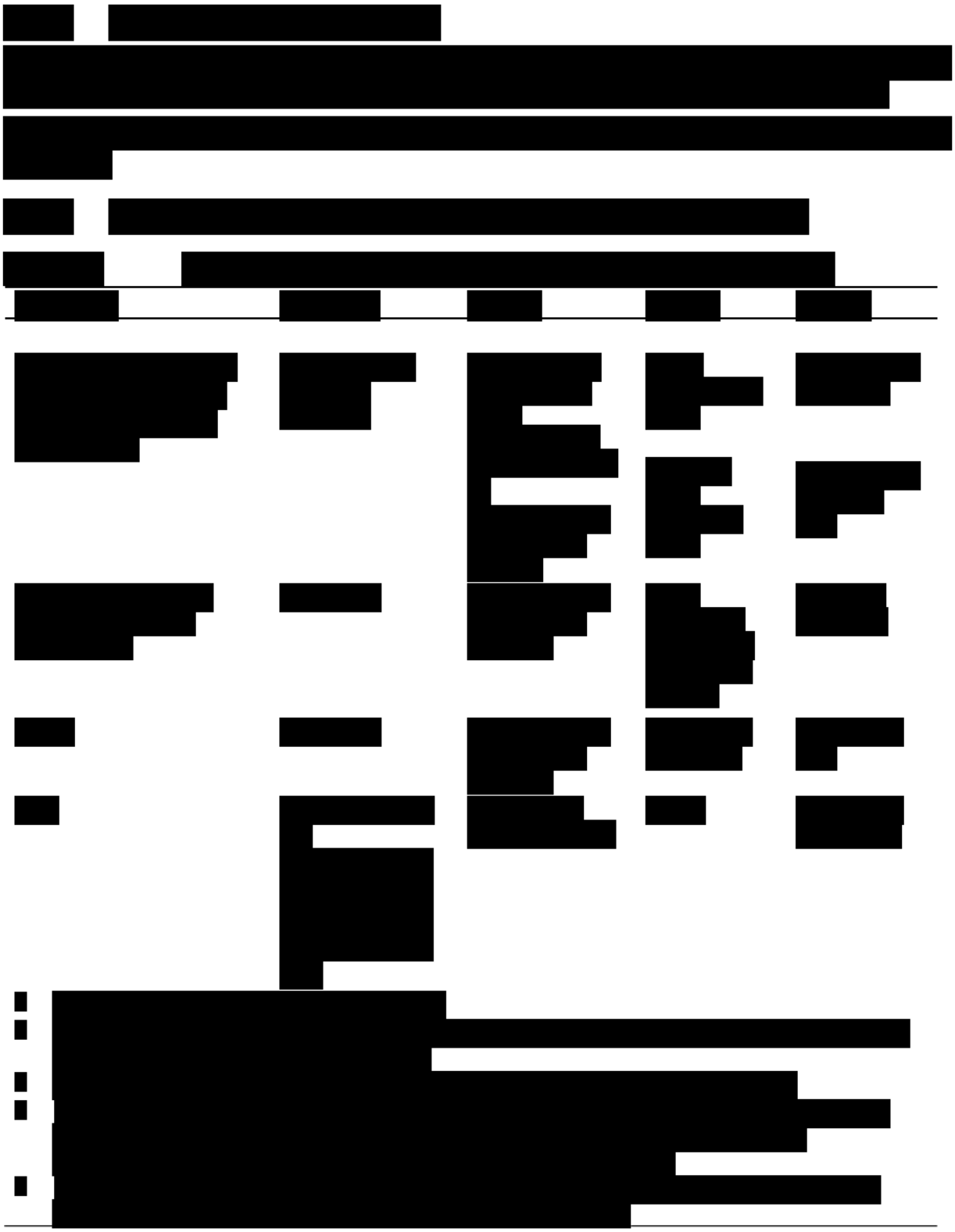
PK parameters for INC280, EGF816 will be calculated using noncompartmental methods based on FPAS-INC and FPAS-EGF. PK parameters including but not limited to those described in Table 2-7 will be summarized. AUCtau will only be summarized for INC280. Only median values and ranges will be given for Tmax. The PK parameters considerd primary are AUCtau, AUClast,, Cmax, and Tmax. Other PK parameters (CL/F, Vz/F, T1/2, Cmin) are considered as secondary. All PK parameters will be listed.

[redacted]

Table 2-7 PK parameters – descriptive statistics

Parameters	Descriptive statistics
AUClast, AUCtau, Cmax, Tmax	N, Mean, standard deviation, CV% mean, geometric mean, CV% geometric mean, median, minimum and maximum
CV% = coefficient of variation (%) = (sd/mean)*100 CV% geometic mean = sqrt (exp (variance for log transformed data)-1)*100	

[redacted]



[redacted]

2.11 Patient reported outcomes

Not applicable.

[redacted]

2.13 Interim analyses

Not applicable.

3 Sample size calculation

The statistical set-up is described in protocol Section 10.4.2 and details about operating characteristics are described in protocol Appendix 3. To have satisfactory operating characteristics, the minimum number of patients at the final established combination dose in each group specified below will be required. The justification for sample size of each group is given below:

Group 1: Nivolumab and EGF816

With a sample size of 40 patients, including potentially 15% drop-outs and loss to follow-up per patient-year prior to cut-off for primary CSR:

- If the true PFS rate at 6 months is low at 55%, the probability to wrongly declare success is low at 0.02;
- If the true PFS rate at 6 months is moderate at 75%, the probability to correctly declare success is high at 0.81;
- If the true PFS rate at 6 months is high at 85%, the probability to correctly declare success is very high at 1.

Such operating characteristics are satisfactory.

Group 2: Nivolumab and INC280

Sub-group A: High cMet

With a sample size of 20 patients, including potentially 15% drop-outs and loss to follow-up per patient-year prior to cut-off for primary CSR:

- If the true PFS rate at 6 months is low at 35%, the probability to wrongly declare success is low at 0.05;
- If the true PFS rate at 6 months is moderate at 55%, the probability to correctly declare success is high at 0.73;
- If the true PFS rate at 6 months is high at 65%, the probability to correctly declare success is very high at 0.95.

Such operating characteristics are satisfactory.

Sub-group B: Low cMet

With a sample size of 30 patients, including potentially 15% drop-outs and loss to follow-up per patient-year prior to cut-off for primary CSR:

- If the true PFS rate at 6 months is low at 25%, the probability to wrongly declare success is low at 0.02;
- If the true PFS rate at 6 months is moderate at 45%, the probability to correctly declare success is high at 0.80;
- If the true PFS rate at 6 months is high at 55%, the probability to correctly declare success is very high at 0.98.

Such operating characteristics are satisfactory.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

Not applicable.

6 References

Not applicable.