NOVARTIS

Clinical Development

EGF816, INC280, Nivolumab

Protocol 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

Document type	Amended Protocol Version
EUDRACT number	2014-003731-20
Version number	08 (Clean)
Development phase	II
Document status	Final
Release date	12-Mar-2020

Template version 02-Dec-2013

[redacted]

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List of abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BCG	Bacillus Calmette-Guerin
b.i.d.	*bis in diem*/twice a day
BLRM	Bayesian Logistic Regression Model
BSA	Body Surface Area
CDP	Clinical Development Plan
Cmax	Maximum concentration
CNS	Central Nervous System
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common criteria terminology for Adverse Events
DCR	Disease control rate
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology Chief Medical Office and Patient Safety (CMO&PS)
ECG	Electrocardiogram
EGFR wt	EGFR wild-type
FISH	Fluorescence In Situ Hybridization
GCN	Gene Copy Number
GGT	Gamma-glutamyl transpeptidase
HBV	Hepatitis B virus
HCV	Hepatitis C Virus
HGF	Hepatocyte Growth Factor
i.v.	intravenous(ly)
ICH	International Conference on Harmonization
ID	Infectious Disease
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IRB	Institutional Review Board
LFT	Liver function test
MTD	Maximum Tolerated Dose
NSCLC	Non-Small Cell Lung Cancer
o.d.	*omnia die*/once a day
ORR	Overall Response Rate

[redacted]

PBMC	Peripheral Blood Mononuclear Cells
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression Free Survival
p.o.	*per os*/by mouth/orally
PHI	Protected Health Information
PPI	Proton Pump Inhibitor
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RDE	Recommended dose for expansion
REB	Research Ethics Board
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
SJS	Stevens-Johnson Syndrome
SOP	Standard Operating Procedure
T3	Triiodothyronine
T4	Thyroxin
TBIL	Total Bilirubin
TEN	Toxic Epidermal Necrolysis
TSH	Thyroid-stimulating hormone
Tmax	Time to reach maximum concentration
TTP	Time to Progression
ULN	Upper Limit of Normal
UNK	Unknown
WBC	White Blood Cells
WT	Wild type
WCLC	World Congress on Lung Cancer

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biological samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
EGFR wt	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.
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival

[redacted]

Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently discontinues study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of Consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Protocol summary:

Protocol number	CEGF816X2201C
Title	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
Brief title	Study of efficacy and safety of Nivolumab in combination with EGF816 and of Nivolumab in combination with INC280 in patients with previously treated non-small cell lung cancer
Sponsor and Clinical Phase	Novartis and Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To determine the efficacy and safety of Nivolumab in combination with EGF816 and of Nivolumab in combination with INC280 in previously treated Non-Small Cell Lung Cancer (NSCLC) patients
Primary Objective(s) and Key Secondary Objective	To assess 6 month PFS rate of Nivolumab in combination with EGF816 in EGFR mutated NSCLC patients and of Nivolumab in combination with INC280 in patients with EGFR wild-type (wt) NSCLC
Secondary Objectives	Objective 1: To assess clinical activity of Nivolumab in combination with EGF816 and of Nivolumab in combination with INC280 as measured by progression free survival, overall response rate, disease control rate and overall survival. Objective 2: To characterize the safety and tolerability of Nivolumab in combination with EGF816 and of Nivolumab in combination with INC280
Study design	Open label, phase II study including a safety monitoring cohort
Population	The study will be conducted in patients with histologically and/or cytologically confirmed advanced, unresectable and/or metastatic NSCLC
Inclusion criteria	• Advanced metastatic and/or unresectable NSCLC • Measurable disease as determined by RECIST version 1.1 • ECOG performance ≤2 • Patients in Group 1: confirmed T790M EGFR mutation • Patients in Group 2: confirmed EGFR wt
Exclusion criteria	• For Group 1: Patients who have received more than one prior line of EGFR TKI therapy • For Group 2: Previous treatment with a cMet inhibitor or HGF-targeting therapy • Prior treatment with PD1/PD-L1 targeting therapies • Patients who require emergent use of systemic steroids, emergent surgery and/or radiotherapy • Patients with interstitial lung disease • Patients with any known or suspected current or past history of autoimmune disease
Investigational and reference therapy	• Nivolumab • INC280 • EGF816

[redacted]

Efficacy assessments	• Tumor response assessment per RECIST version 1.1 • Progression free survival • Overall response • Overall survival
Safety assessments	• Incidence and severity of adverse events • Physical examination • Vital signs • Weight • ECOG performance status • Laboratory evaluations • Radiological examinations • Cardiac assessments
Other assessments	• (Secondary for safety monitoring cohort) Nivolumab, EGF816, INC280 pharmacokinetic evaluations [redacted]
Data analysis	For the safety monitoring cohort, a review of clinical and laboratory data will be used before enrolling additional patients. A Bayesian design will be used to determine PFS rate at 6 months in each group.
Key words	Nivolumab, EGF816, INC280, PD-1, NSCLC

[redacted]

Amendment 8 (12-Mar-2020)

Amendment rationale

The main purpose of this protocol amendment is to introduce the timing for primary Clinical Study Report (CSR) and its impact on study conduct. The cut-off date for the primary analysis will take place after 12 months has elapsed from last patient first treatment. By then, the ongoing patients will have been on treatment for between 12 and 60 months, and there will be sufficient data for both primary and secondary efficacy objectives evaluation. The duration of disease progression follow-up period is modified to remove the efficacy assessment after 12 months from last patient first treatment. This amendment also aims to reduce the assessment burden for patients while maintaining access to study treatment and monitoring safety. Besides, the definition of end of study is refined to allow earlier closure of study by incorporating language to include option for ongoing patients in Group 2, who are eligible and are still deriving clinical benefit in the opinion of the investigator, to transfer to a Novartis roll-over study or an alternative treatment option after the data cut-off for primary analysis as a possible means to ensure continued access to study treatment.

In addition, the dose modification guidance and adverse event management algorithm have been updated based on new information from INC280 Investigator Brochure edition 11 and Nivolumab Investigator Brochure edition 18. This amendment also implements a maximum duration of 2 years for Nivolumab treatment as per emerging data from clinical trials conducted with Nivolumab.

Other minor changes and corrections were made throughout the protocol for consistency and/or clarifications.

Study Update

This study is currently ongoing. Enrollment in Group 1 has been halted since 17-Dec-2015. Enrollment in Group 2 has been halted since 16-Apr-2019. In total, 64 patients have received study treatment. As of 16-Jan-2020, all patients in Group 1 have discontinued study treatment and there are 4 patients remain on treatment in Group 2 (INC280 + Nivolumab). When this amendment becomes effective, the 2 patients in Group 2 who have received Nivolumab beyond 2 years will discontinue Nivolumab treatment and continue on INC280 alone. These 2 patients are immediately eligible for transfer to a Novartis roll-over study or an alternative treatment option after the data cut-off for primary analysis. There is 1 patient in Group 2 who have previously discontinued INC280 and have been receiving Nivolumab alone. This patient will discontinue Nivolumab treatment, have an end of treatment visit and continue with the safety and survival follow-up as per Table 7-1b. The remaining patient is still receiving INC280 + Nivolumab combination treatment and will reach the 2-year cap in Apr-2021. By then, this patient will also become eligible for transfer to a Novartis roll-over study or an alternative treatment option.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

[redacted]

- Section 1.2.3.2.2: updated to include the recent events of myocarditis and hepatitis experienced by 1 patient who received INC280 in combination with PDR001 (a PD-1 inhibitor) in Novartis study CPDR001J2201
- Section 2.5: added this section to illustrate the rationale for implementing a maximum duration of 2 years for Nivolumab treatment.
- Section 4.1: updated the definition of end of treatment period, added language to include the possibility of patients being transferred to a Novartis roll-over study or an alternative treatment option after the data cut-off for primary analysis, added that the maximum treatment duration of Nivolumab cannot exceed 2 years, added instruction on treatment and study visit arrangement following the approval of protocol amendment 08, and clarified that for patients who transfer to a Novartis roll-over study will not enter the safety follow-up period.
- Section 4.3: updated the definition of end of study and removed an obsolete definition on when to perform primary analysis for purpose of clarification.
- Section 6.1: added language to specify that the maximum duration of Nivolumab treatment will be 2 years and instruction on treatment and study visit arrangement following the approval of protocol amendment 08.
- Table 6-2: dose modification criteria for myocarditis have been added.
- Section 7.1: added Table 7-1b for a simplified study assessment schedule, added instruction to refer to Table 7-1b after protocol amendment 08 is approved, and modified the duration of disease progression follow-up period and the definition of end of survival follow-up period.
- Section 7.1.3: updated the definition of end of treatment period and added instruction on treatment and study visit arrangement following the approval of protocol amendment 08.
- Section 7.1.4: added language to specify that patients who transfer to a Novartis roll-over study or an alternative treatment option to continue provision of study treatment will complete end of treatment procedures.
- Section 7.1.4.1: updated language to describe the data that would have been collected at subsequent visits will be considered missing, to specify all efforts should be made to complete a final assessment upon withdrawal of consent, and how is Novartis handling the already collected study information.
- Section 7.1.5: added language to specify that patients who transfer to a Novartis roll-over study or an alternative treatment option to continue provision of study treatment will not complete the follow-up for safety, disease progression and survival.
- Section 7.2: amended to reduce assessments, to remove central review of ECG, to remove PK and immunogenicity samples collection, to inform no efficacy assessments will be done after 12 months has elapsed from last patient first treatment for the still ongoing patients and patients in disease progression follow-up. Table 7-4b is added for a simplified local clinical laboratory parameters collection plan.
- Section 10: added definitions of the timing of primary analysis.
- Section 10.4: updated the timing of primary analysis.
- Appendix 5: updated the immuno-oncology related adverse event management algorithm.

[redacted]

- Other minor changes and corrections were made throughout the protocol for consistency and/or clarifications.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 7 (21-Jun-2018)

Amendment rationale

The main purpose of this protocol amendment is to update the guidelines for EGF816/INC280 dose modification/ discontinuation in the context of non-infectious pneumonitis/interstitial lung disease, to be consistent across different INC280 studies, as requested by a regulatory authority.

Study Status

This study is currently on-going. As of 6-June-2018, 59 patients have been enrolled into this study: 18 in Group 1 (EGF816 + Nivolumab) and 41 in Group 2 (INC280 + Nivolumab). Enrollment in Group 1 has been halted since 17-Dec-2015.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Table 6-2, Dose reduction and interruption criteria: Recommended dose modifications for ILD like events/pneumonitis have been added.
- Section 6.2.2 and Table 6-3, Follow-up for toxicities are updated to include guidance for ILD/pneumonitis.
- Section 14.6, Appendix 6 – Guidelines for EGF816/INC280 dose modification and discontinuation for pneumonitis/ILD have been removed.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

Amendment 6 (29-Jan-2018)

Amendment rationale

The rationale for this amendment is as follows:

- The nivolumab Investigator's Brochure (IB) Edition 16 (Version date 23-Jun-2017) has been updated with new recommendations for management of myotoxicity. In response to a health authority request, this amendment will add these recommendations. Since clinical safety information provided for nivolumab in Section 1.2.3.2.2 is outdated, the single agent safety data were replaced with a reference to the nivolumab prescribing information and the current IB.
- New data on effects of food and concomitant medications on INC280 exposures became available. Therefore, the protocol has been updated accordingly to allow INC280 to be taken with or without food and to update the prohibited concomitant medications and the permitted concomitant medications to be used with caution for Group 2 patients.
- Pneumonitis/interstitial lung disease has been added as a potential risk for INC280.
- Recommendations for discontinuing patients from study treatment versus from only one study drug in the setting of specific adverse events were clarified in Table 6-2.

Study status

This study is currently on-going. As of 07-Dec-2017, 43 patients have been enrolled into this study: 18 in Group 1 (EGF816 + Nivolumab) and 25 in Group 2 (INC280 + Nivolumab). Enrollment in Group 1 has been halted since 17-Dec-2015.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Section 1.2.2.2 Clinical experience – Updated clinical safety text to align with the program standard language for INC280 protocols.

Section 1.2.2.2.2: Updated the clinical pharmacokinetics text for INC280 based on newly available drug-drug interaction (DDI) data and added a statement based on the preliminary PK data from study CINC280A2108 that showed no food effect of high fat meal on INC280 exposure.

Section 5.3 Exclusion Criteria – The following changes were made to this section

- Exclusion criterion 17 was updated to reflect changes in INC280 PK and concomitant medication restriction related changes.
- Exclusion criterion 22 was added to exclude patients with a history of Long QT syndrome or family history of idiopathic sudden death, to align with current standard program exclusion criteria
- Exclusion criterion 23 was added to exclude patients who cannot discontinue medications with a known risk of Torsades de Pointes, to align with current standard program exclusion criteria

[redacted]

Section 6.1.1: Several changes were made to allow administration of INC280 with or without food.

Table 6-2 Criteria for omission, delay, or discontinuation of Nivolumab, EGF816 and INC280 for patients receiving Nivolumab and EGF816 or Nivolumab and INC280—

- Added a dedicated entry for myotoxicity, specifying nivolumab dose delay and specialist referral for any nivolumab-related Grade ≥ 2 myotoxicity and nivolumab discontinuation for nivolumab-related Grade 3 myocarditis or nivolumab-related Grade 4 other myotoxicity
- Where applicable, changed "study drug" to "study treatment" for circumstances in which a patient should be discontinued from study treatment rather than from only one study drug.

Section 6.3.1: Permitted concomitant therapy requiring caution was updated based on the newly available preliminary DDI data from other INC280 studies. Patients receiving INC280 are affected by this change.

Section 6.3.2: Updated text based on available preliminary DDI data from other INC280 studies.

Section 14:

- Appendix 1 and 2 have been updated to reflect recent revisions to prohibited and permitted concomitant therapies for patients receiving INC280. These changes align with the program standard language for INC280 protocols.
- Appendix 6 "Guidelines for EGF816/INC280 dose modification/ discontinuation in the context of non-infectious pneumonitis/interstitial lung disease" the title and the text was updated to include INC280. Where applicable in this section, "study drug" was changed to "study treatment" for circumstances in which a patient should be discontinued from study treatment rather than from only one study drug.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 5 (13-Apr-2017)

Amendment rationale

- The primary purpose of this amendment is to introduce the 150 mg strength of INC280 tablet formulation. This is to allow patients to take a dose of 300 mg when the 50 mg strength is discontinued.
- Further, clarifications have been made to the exclusion criteria for Hepatitis B and Hepatitis C to ensure consistent interpretation. Previously the clarification was included in Appendix 7. With this amendment the key points from Appendix 7 have been included as a clarification note immediately under exclusion criterion 10.
- Updates were made to section 1.2.2, Overview of INC280, subsections 1.2.2.2.1 Clinical Safety and 1.2.2.2.2 Clinical Pharmacokinetics to reflect the recently updated INC280 Investigator's Brochure (IB).
- A requirement was added that pregnancy tests occurring between screening and the 30-day safety follow-up, inclusive, must be serum tests because of the higher sensitivity of serum pregnancy tests as compared to urine pregnancy tests.

Changes for consistency and administrative purposes have also been made where necessary throughout the protocol.

Study status

This study is currently on-going. As of 02-Mar-2017, 27 patients have been enrolled into this study: 18 in Group 1 (EGF816 + Nivolumab) and 9 in Group 2 (INC280 + Nivolumab). Enrollment in Group 1 has been halted since 17-Dec-2015.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Section 1.2.2.2 Clinical experience - Added information to reflect the recently updated INC280 Investigator Brochure (IB).

Section 1.2.2.2.2 Clinical Pharmacokinetics – Updated to include the most recent data

Section 5.3 Exclusion Criteria – Added information to clarify that viral hepatitis screening tests related exclusion apply to all patients.

Section 5.3 Exclusion Criteria – Added a new exclusion criterion related to Gastro Interstinal (GI) function impairment for patients participating in Group 2 (INC280 and Nivolumab combination arm).

Section 6.2.1 Dose modification and dose interruption for EGF816, INC280 and Nivolumab – Table 6-2 updated to include criteria for dose modification of INC280 for nausea, vomiting and peripheral edema.

Section 6.5.1 Study drug packaging and labeling – Added information about the new INC280 strength of 150 mg.

Section 7.1 Visit evaluation schedule – Added serum pregnancy tests.

[redacted]

Section 7.2.2.5.4 Pregnancy and assessments of fertility – Language was updated to require the serum pregnancy tests during the treatment phase.

Section 11.5 – Publication of study protocol and results – Language updated to match recent revisions in the publication policy and the revised new protocol template

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 4 (19-May-2016)

Study status

This study is currently on-going. As of 18-Dec-2015, 22 patients have been enrolled into this study: 18 in Group 1 and 4 in Group 2. Enrollment in Group 1 has been halted since 17-Dec-2015.

Amendment rationale

The primary purpose of this amendment is to allow the exploration of the immunomodulatory activity of INC280 in patients with NSCLC. It has been demonstrated that inhibition of hepatocyte growth factor (HGF)/cMet signaling in monocytes may enhance anti-tumor T-cell activation (Rutella et al., 2006). Since patients whose NSCLC cells lack high cMet are not expected to derive benefit from INC280 treatment on the basis of cMet inhibition in tumors, this hypothesis can be explored in patients with NSCLC whose tumor cells have low or undetectable cMet expression (hereafter referred to as cMet low). This amendment will therefore expand the eligibility of Group 2 patients (INC280 plus nivolumab) to include patients with NSCLC without high cMet levels (i.e., any level of cMet will now be permitted). The study will thus enroll 2 sub-groups within Group 2 of EGFR wt patients, a high cMet sub-group and a low cMet sub-group. In patients with cMet low NSCLC, improvements in response compared to historical data for nivolumab treatment alone could reasonably be attributed to inhibition of cMet in monocytes. [redacted]

In addition, as NSCLCs harboring activating cMet mutations have been shown to be sensitive to cMet inhibition (Paik et al 2015, Frampton et al 2014), to identify all Group 2 patients whose tumors might be sensitive to cMet inhibition, tumors from Group 2 patients will be retrospectively tested for activating cMet mutations.

This amendment also introduces the provision for study treatment to be temporarily interrupted for palliative treatment of symptomatic central nervous system (CNS) or bone lesions with non-invasive therapy, such as radiation or radiofrequency ablation. The rationale for this is to allow patients who are otherwise benefitting from study medications to stay on the study despite requiring palliative treatment of symptomatic lesions.

The frequency of radiological efficacy assessments after cycle 24 have been decreased in response to an institutional review board request to decrease cumulative radiation exposure for patients who may remain on study longer than 24 cycles.

To optimize the management of liver toxicities and be consistent across the different INC280 studies, this protocol amendment provides additional guidance to investigators for the management of liver toxicities and specifically work-up guidelines for potential Drug Induced Liver Injury (DILI) cases, which were implemented based on the previously described single

[redacted]

case of a serious, unexpected, possibly related adverse event of abnormal liver function tests (LFTs) that met the lab criteria of Hy's Law. Patients with increased AST/ALT and total bilirubin values that may be indicative of potential DILI, should be considered as clinically important events; therefore, specific guidance for actions to be taken on the study treatment (e.g. discontinuation) and for monitoring of LFTs have been implemented and clarified.

The eligibility criteria and dose modification guidelines for the amylase and lipase have been updated to optimize the management of such toxicities and be consistent across the different INC280 studies.

In addition, based on new PK data it is suggested that the concomitant use of Proton Pump Inhibitors (PPIs) is unlikely to impact the efficacy of INC280, therefore the PPI restriction can be removed from this protocol for patients requiring PPI gastric protection treatment. Moreover, requirements on other acid reducing agents (gastric acid modulators and H2 receptor antagonists) can also be removed.

The list of prohibited and to be used with caution medications for INC280 has also been updated based on the latest internal DDI guidance and has been modified to include drugs with known risk of causing QTc prolongation.

Changes for consistency and administrative purposes have also been made where necessary throughout the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 1.1: Added text "In addition to its role within tumor cells, cMet signaling also plays a role in immune cells. Specifically, HGF/cMet signaling in monocytes has been demonstrated to shift their differentiation toward regulatory dendritic cells, which in turn inhibit T cell activation (Rutella 2006). Therefore, inhibition of cMet in monocytes may result in enhanced anti-tumor T cell responses".
- Section 1.2.1.2: Updated the clinical experience related text for EGF816 based on the updated IB released in April 2016.
- Section 1.2.2.2.1: Updated the clinical experience related text for INC280 based on the updated IB released in Nov 2015.
- Section 1.2.3.2.2: Clarified the cause of death for the patient who died after experiencing the AE of toxic epidermal necrolysis.
- Section 2.2: "…adult patients with cMet positive non-small cell lung cancer" was changed to "….adult patients with EGFR-wild-type non-small cell lung cancer". This change has been made in several places within this amendment due to the decision to allow patients with EGFR-wild-type mutation to enroll regardless of cMet expression in the tumor sample. Additional clarifications and editorial changes were made to the last paragraph in this section.

[redacted]

- Section 4.1: Text was updated to reflect the plan to sub-divide Group 2 (EGFR-wild-type) into Sub-group A (high cMet) and Sub-group B (low cMet). Additional changes to this section include insertion of a reference to Section 5.1 for the target enrollment and deletion of repetitive text.
- Section 5.1: Clarified that enrollment in Group 1 has been halted. Target enrollment in group 2 is now updated to at least 50, such that approximately 20 patients with high cMet are enrolled in Sub-group A and approximately 30 patients with low cMet are enrolled in Sub-group B. Though cMet criteria for cMet high have not changed, the previous version of the protocol did not provide the cMet requirement to qualify for high cMet, this has now been added.
- Section 5.3: Deleted exclusion criteria related to the use of long acting proton pump inhibitors. Safety laboratory related exclusion criteria were updated for patients being screened for Group 2. Additional clarifications were made to other exclusion criteria to match revised INC280 concomitant medication restrictions.
- Section 6.2.1: Clarified the circumstances under which a patient must be discontinued from EGF816 or INC280 following treatment interruption. Clarified exceptions to the requirement to discontinue nivolumab following a nivolumab dose interruption of >6 weeks.
- Table 6-2: Clarification and editorial changes were made to this table.
- Section 6.2.2: This section was added to provide recommendations on follow-up evaluations for patients experiencing hepatic toxicities.
- Section 6.2.3: Added a section to provide guidance on follow-up on potential drug induced livery injury observed in patients.
- Section 6.3: Clarified the requirements to taper the dose of systemic corticosteroids prior to resuming nivolumab.
- Section 6.3.1: Several changes have been made to match recent updates to permitted concomitant therapy for patients receiving INC280 treatment. Also clarified that Localized palliative non-invasive therapy is allowed and provided instructions on holding the study drugs for patients who require such therapy.
- Section 6.3.2: Several changes have been made to match recent updates to prohibited concomitant therapy for patients receiving INC280 treatment.
- Table 7-1: Visit schedule was updated to reflect additional biopsies and blood collections for new analysis added with this amendment.
- Section 7.1.1: Text updated to clarify the molecular pre-screening sample requirement and the analysis expected to be performed on that sample.
- Table 7-2: Frequency of imaging related assessments was reduced starting with Cycle 13.
- Table 7-11: Updated most of the table to reflect additional biomarker samples collections and the planned analysis.
- Section 7.2.4.1: Biomarker tumor assessment section updated to reflect additional assessments and time points added with this amendment.
- Section 7.2.4.2: Inserted text related to additional blood sample collection for cytokine assessments at various time-points.

[redacted]

- Section 8.1.1: minor changes made to match the updated template.
- Section 8.2.2: Text updated to match-up with revised template that adds flexibility of reporting SAE via an electronic tool when it becomes available.
- Section 8.3: Clarifications added to the text in the pregnancies section
- Section 10: clarification added that Sub-groups A and B within Group 2 will be treated as separate treatment groups for the purpose of statistical analysis. This clarification has also been added to other sub-sections within Section 10.
- Section 10.4.2: Section updated to reflect changes made with this amendment.
- [redacted]
- Section 10.8: Sample size calculation has been updated to reflect changes made with this amendment.
- Section 13: Reference added
- Section 14: Appendix 1 and 2 have been updated to reflect recent revisions to prohibited and permitted concomitant therapies for patients receiving INC280. Appendix 3 has been updated with hypothetical datasets to support some of the changes made with this amendment.
- Section 14.3.3.2: This section has been updated

IRBs/IECs

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[redacted]

Amendment 3

Amendment rationale

The primary purpose of this amendment is to implement changes that were introduced with two Urgent Safety Measures (USMs) that were issued on December 17, 2015 and January-28, 2016. The first USM was issued after a fatal case of toxic epidermal necrolysis (TEN) occurred in a patient in Group 1 (EGF816 plus nivolumab). Although TEN is reported as a rare adverse event associated with nivolumab and is listed within the informed consent form for this study, Novartis could not exclude the possibility that this adverse event was related to the combination of EGF816 and nivolumab. Novartis therefore instituted a temporary halt to enrollment into Group 1 (EGF816 plus nivolumab), effective December 10, 2015, to allow for a thorough review of available data. Novartis also issued an USM to provide guidance on the re-consent and management of ongoing patients in Group 1 (EGF816 plus nivolumab), and to provide updated skin toxicity management guidelines for Group 1 patients.

The second USM was issued after a fatal case of pneumonitis occurred in a patient in Group 1. Pneumonitis is an expected adverse event associated with nivolumab monotherapy. According to the U.S. Prescribing Information, pneumonitis, including interstitial lung disease, was reported in 3.4% of patients treated with single-agent nivolumab in a phase 3 study of metastatic non-squamous NSCLC. The fatal case occurring in Group 1 of this study (CEGF816X2201C) was the second case of pneumonitis in 18 patients treated in this group; in addition, a case of interstitial lung disease was also reported in another patient in this group. Pneumonitis/interstitial lung disease is a rare adverse event associated with EGF816 monotherapy, having been reported in 2 patients of 146 treated with the single agent as of January 19, 2016. These data suggest that the rate of pneumonitis may be higher for EGF816 in combination with nivolumab than for nivolumab alone.

To minimize the risk to patients participating in the CEGF816X2201C study, the following changes have been made to the protocol:

- Halt of enrollment to Group 1 (EGF816 plus nivolumab).
- Permanent discontinuation of nivolumab for all ongoing patients in Group 1 (EGF816 plus nivolumab). Ongoing patients in Group 1 may remain on EGF816 as a single agent after re-consent of the patient.
- Addition of a provision that if at any time during the study Novartis determines that a lower dose level of EGF816 or INC280 should be explored, enrollment to the ongoing higher dose cohort may be stopped and ongoing patients may have their dose of EGF816 or INC280 reduced.
- Altering the dose-modification table (Table 6-2) to refer to a separate section (Section 6.2.1.1) for separate skin toxicity management guidelines for patients in Groups 1 and 2.
- Moving Appendix 6 to Section 6.2.1.1 and reflecting the recommendation that all rashes in Group 1 patients should be considered possibly related to EGF816 and nivolumab, and that skin toxicity grade-specific actions should be taken with both drugs as defined in Table 6-4. Separate guidance for non-maculopapular rashes was also removed.

[redacted]

- Changing Table 14-12 to Table 6-4 and providing grade-specific skin toxicity management guidelines appropriate to the presumption that all rashes are attributable to both EGF816 and nivolumab.

Changes to the protocol

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List of abbreviations

Abbreviations added for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Section 1.2.3.2.2 Clinical Safety – Added descriptions of the case of TEN and pneumonitis, and the rationales for their possible attribution to the combination of EGF816 and nivolumab.

Section 4.1 Description of Study Design –

Added the statements that, as of Amendment 3, enrollment to Group 1 has been halted and ongoing patients in Group 1 must be discontinued from nivolumab.

Added the provision that if at any time during the study Novartis determines that a lower dose level of EGF816 or INC280 should be explored, enrollment to the ongoing higher dose cohort may be stopped and Novartis may require the dose of EGF816 or INC280 to be reduced for any ongoing patients.

Table 6-2 Criteria for omission, delay, or discontinuation of Nivolumab, EGF816 and INC280 for patients receiving Nivolumab and EGF816 or Nivolumab and INC280 was updated

Created 6.2.1.1. Guidelines for prevention and management of rash/skin toxicities. Section 6.2.2 deleted bullet “Patients who have not experienced a Grade 3 Nivolumab related skin AE may resume treatment in the presence of Grade 2 skin toxicity

Section 8.1.1 Added a statement permitting Novartis to centrally review any remaining clinical sample obtained from a patient as part of the evaluation of an adverse event.

Section 10.1.3 Per-Protocol Set, under bullet Group 1 patients, a sub-bullet “or have received agents targeting EGFR T790M” has been deleted. Under bullet Group 2 patients, “(adenocarcinoma)” has been deleted from the first bullet.

Section 14.6, Appendix 6 Guidelines for prevention and symptomatic care of rash/skin toxicities in Group 1 patients -

- Moved to Section 6.2.1.1
- Updated title to “Guidelines for prevention and management of rash/skin toxicities”
- Added guidelines for education of patients on the importance of notifying investigators immediately if a skin rash occurs and on preventative care of the skin.
- Added instructions for investigators to call Novartis if a patient develops a rash of Grade 2 or higher
- Added instructions to attribute all rashes in Group 1 patients to both EGF816 and nivolumab, and to refer to Table 6-4 for management of rashes and for actions to be taken with EGF816 in the event of rash

[redacted]

- Table 14-11 Guidelines for prevention and symptomatic care of rash/skin toxicities, moved to Section 6.2.1.1 and changed the table number and title to "Table 6-3 Guidelines for prevention and symptomatic care of rash/skin toxicities for all patients"
- Table 14-12 Management and dose modification for maculopapular rash moved to Section 6.2.1.1 and changed the table number and title to "Table 6-4 Guidelines for dose modification and management related to rash for Group 1 patients"
- Modified the table to include actions to be taken with EGF816 and nivolumab as well as additional management guidelines for each grade of rash
- Removed Table 14-13 Management and dose modification for other rashes including acneiform rash as all rashes in Group 1 patients are to be managed similarly

Section 14.7 Appendix 6 Guidelines for the Management of Non-Infectious Pneumonitis/Insterstitial Lung Disease—This section is now Section 14.6. Modified the title to "Appending 6 Guidelines for EDG816 dose modification/ discontinuation in the context of non-infectious pneumonitis/ interstitial lung disease. Added the statement that all patients should be educated on the importance of notifying the investigator immediately with any new respiratory symptoms. Removed two columns "Required investigations" and "Management of pneumonitis".

IRB/IEC Approval

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[redacted]

Amendment 2

Amendment rationale

The primary purpose of this amendment is to address changes requested by Health Authorities. The changes include:

- Clarifying the definition of "toxicity as independent of study drug" as it appears in the heading of the second column in Table 6-2 Criteria for interruption, omission, delay, re-initiation and discontinuation of Nivolumab, EGF816 and INC280 for patients receiving Nivolumab and EGF816 or Nivolumab and INC280"
- Modify the protocol guidelines for hepatotoxicity for cases meeting Hy's Law criteria
- Provide guidelines for dose modification or discontinuation for EGF816-related interstitial lung disease

In addition, the following changes have been made:

- Update guidelines for dose modifications, dose interruptions and discontinuation of EGF816, INC280, and nivolumab due to hepatotoxicity associated with isolated elevations of AST or ALT, or total bilirubin
- Provide clarification to criteria for resuming nivolumab treatment after dose delay
- Update list of prohibited concomitant medications to include live vaccines, for patients dosed with EGF816
- Added additional guidance for managing EGF816-associated rash

Other sections of the protocol have been modified to provide further granularity and clarity.

Additionally, administrative and typographical errors have been corrected throughout the document.

Changes to the protocol

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List of abbreviations

Abbreviations added for laboratory tests and tuberculosis vaccine

Section 6.2.1 Dose modification and dose interruption for EGF816, INC280 and Nivolumab – For either EGF816 or INC280 – Clarified text to allow a maximum of two dose interruptions per patient

Table 6-2 – Criteria for interruption, omission, delay, re-initiation and discontinuation of Nivolumab, EGF816 and INC280 for patients receiving Nivolumab and EGF816 or Nivolumab and INC280

- Update table title to "Criteria for omission, delay, or discontinuation of Nivolumab, EGF816 and INC280 for patients receiving Nivolumab and EGF816 or Nivolumab and INC280"

[redacted]

- Clarified table header to define toxicity during a cycle of therapy as "related to EGF816 or INC280" rather than "independent of study drug"
- Clarified "Bilirubin" and "AST or ALT" sections as "Isolated Total Bilirubin elevation" and "Isolated AST or ALT elevation"
- Added additional guidance for isolated total bilirubin and isolated AST or ALT elevation associated with EGF816, INC280, and nivolumab
- Provided clarification and additional guidance for combined elevations of AST or ALT and total bilirubin toxicities associated with EGF816, INC280, and nivolumab
- Additional clarifications and administrative updates as required

Section 6.2.2 Criteria to resume treatment with Nivolumab

- Updated title to "Criteria to resume treatment with Nivolumab after Dose Delay"
- Removed exception "patients with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued"

Section 6.3.2 Prohibited concomitant therapy – Added "live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines) should not be administered while a patient is dosed with EGF816 and for 30 days after the last dose of EGF816"

Appendix 2 Prohibited Concomitant Medications – Added live vaccines, e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines

Appendix 5 Management Algorithms – various administrative changes made

Appendix 6 Guidelines for prevention and symptomatic care of rash/skin toxicities – Updated to include adverse event management and action taken with study drug and dose modifications for EGF816-related maculopapular rash and other rashes including acneiform rash

Appendix 6 Guidelines for the management of non-infectious pneumonitis/interstitial lung disease – Updated to include action taken with study drug and dose modifications

Appendix 7 Guidelines for Viral Hepatitis testing and for ongoing and new patients – Provided clarification that eligible patients who are positive for HBsAb and negative for HBV-DNA should also have a history of Hepatitis B vaccination

IRB/IEC Approval

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

Amendment 1

Amendment rationale

The primary purpose of this amendment is to address changes requested by Health Authorities. The changes include:

- Providing additional guidelines for hepatic adverse event management for EGF816 and INC280 study medications.
- Clarifying that in the United States, in the absence of an approved investigational drug exemption (IDE), assays for determination of cMet dysregulation will be performed only on archival samples.
- Providing updated contraception guidance following nivolumab treatment, in alignment with guidelines provided in the nivolumab Investigator Brochure.
- Adding simvastatin to the list of prohibited concomitant medication since simvastatin is a substrate of CYP3A4, CYP2C8 and OATP1B1.
- Excluding patients with a history of allergy or hypersensitivity to nivolumab drug components.
- Implementing HIV testing at screening for patients in Germany.

In addition, the following changes have been made:

- Clarifying tests to be conducted at screening for Hepatitis B/C based on the Urgent Safety Measures issued on 8-Jul-2015 to all sites and investigators participating in the study CEGF816X2201C
- Providing new clinical safety information for EGF816 and INC280.
- Providing guidelines for prevention and symptomatic care of rash/skin toxicities and updating guidelines for skin toxicity management and dose modification.
- Providing additional guidelines for monitoring and management of pneumonitis and interstitial lung disease.
- Clarifying that samples collected from patients before withdrawal of consent can be retained and analyzed at future dates and results can be used for reporting purposes.
- Clarifying that alternative dose cohorts may be opened after reviewing the data from the safety monitoring cohort during or/and at the end of the six week period after discussion and agreement between Novartis and investigators

Other sections of the protocol have been modified to provide further granularity and clarity.

Additionally, administrative and typographical errors have been corrected throughout the document.

Changes to the protocol

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List of abbreviations

[redacted]

Abbreviations added for biological samples, withdrawal of consent and updated abbreviations for study treatment discontinuation.

Section 1.2.1.1 Clinical experience

Updated safety information for EGF816 based on new data from clinical trial CEGF816X2101.

Section 1.2.2.2.1 Clinical experience

Updated safety information for INC280 based on new data from clinical trial CINC280X2202.

Section 2.2 Rationale for the study design

Clarification added that alternative dose cohorts may be opened after reviewing the data from the safety monitoring cohort during or/and at the end of the six week period after discussion and agreement between Novartis and investigators

Section 4.1 Study design

Clarification added that if there are no safety concerns from the safety monitoring cohort and a lower dose is selected based on other ongoing studies, no additional safety monitoring cohort is needed and enrollment may proceed to reach the planned sample size at the selected lower dose. In addition, clarification added to state that based on emerging data, the safety-review meeting between Novartis and principal investigators may take place prior to completion of six weeks for study continuation to address potential safety concerns.

Molecular pre-screening – Clarification added that tumor tissue must be submitted at pre-screening for determination and/or confirmation of protocol specific pre-requisite genetic alterations.

Section 5.2 Inclusion criteria –

Removed requirement of a mandatory pre-screening biopsy from criterion #6.

Section 5.3 Exclusion criteria - Modified criteria #19 and #20 to update contraception period for women of child bearing potential and for men who are sexually active with women of child bearing potential.

Added criterion #5 to state that patients with history of allergy or hypersensitivity to nivolumab study drug components will be excluded from the study

Section 6.2.1 Table 6-2

- Added clarification for dose modification for hepatic adverse event management for EGF816 and INC280
- Added clarification for dose modification for rash guidelines.

Section 6.3.2 Prohibited concomitant therapy.

Addition of Simvastatin, a substrate of CYP3A4, CYP2C8 and OATP1B1, as a prohibited medication for INC280/Nivolumab combination.

Section 7 Visit schedule and assessment.

- Deleted blood sampling at cycle 6 for Nivolumab PK for consistency with Table 7-8 in Section 7.2.3.2.

[redacted]

- Clarified that PK samples will be collected at disease progression for consistency with Tables 7-6 to 7-10
- Added footnote to indicate that vital sign assessment is only required for patients at C2D14.
- Added a footnote indicating that for United States (US) patients, only archival tumor sample will be used for determination/confirmation of cMet dysregulation.
- Clarified that fresh biopsy will not be repeated at screening if performed at pre-screening.
- Updated whole blood sampling for genetic analysis for consistency with text in Table 7-11.
- Added HIV testing at screening for patients in Germany.
- Added Hepatitis B/C testing at screening to Table 7-1.
- Edited/added footnotes accordingly.

Section 7.1.4.1 Added a section for withdrawal of consent - Text added to clarify that all samples/results collected from patients before withdrawal of consent can be retained and analyzed at future dates and results can be used for reporting purposes.

Section 7.1.4.2 Criteria for premature withdrawal updated for clarity.

Section 7.1.5 Follow up period

Added text to clarify that data collected should be added to Adverse Event CRF and concomitant medication CRF.

Section 7.1.6 Added a section for Lost to follow up

Added text to clarify that procedures for loss to follow up.

Section 7.2.2.5 Table 7-4 Local clinical laboratory parameters collection plan

- Clarified tests to be conducted at screening for Hepatitis B/C based on the Urgent Safety Measures issued on 8-Jul-2015 to all sites and investigators participating in the study CEGF816X2201C
- Added HIV test at screening for patients in Germany.

Section 7.2.3.2 Pharmacokinetic and immunogenicity sampling schedule - Added a blood sampling timepoint to Table 7-8 for Nivolumab immunogenicity and pharmacokinetics.

Section 7.2.4 Biomarkers Table 7-11 - Updated to specify that cMet detection/confirmation of cMet dysregulation will be performed on archival tumor samples only for US patients.

Section 10 Statistical methods and data analysis

Added text to clarify that 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.

Appendix 1 List of concomitant medications to be used with caution - Addition of P-gp substrate (dabigatran) and CYP2D substrate (perhexiline) and deletion of tizanidine.

Appendix 2 Prohibited Concomitant Medications - Addition of simvastatin to the list.

[redacted]

Appendix 6 Guidelines for prevention and symptomatic care of rash/skin toxicities was added
Appendix 7 Guidelines for management of non-infectious pneumonitis/interstitial lung disease was added.

Appendix 8 Guidelines for screening and monitoring for hepatitis B and C virus were added.

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[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Lung cancer is a major public health problem that accounts for 13% (1.6 million) of the total cancer cases and 18% (1.4 million) of cancer deaths (Jemal et al 2011). The American Cancer Society estimated 159,390 deaths from lung cancer in the United States for 2009 alone (Sangodkar et al 2010). In China, there were 497,908 new cases and 428,936 deaths in 2005, the highest for any malignant tumor (Wu et al 2007). Despite the identification of specific targets (1) progression on therapeutic agents designed to inhibit those targets occurs (e.g., EGFRT790M); (2) development of additional therapeutic agents that inhibit other targets is critical (e.g., cMet); and (3) development of combinations of targeted therapies in conjunction with immunotherapy is necessary.

Epidermal growth factor receptor (EGFR) has been proven to be a key therapeutic target for lung cancer. EGFR inhibitors, like erlotinib (Tarceva) and gefitinib (Iressa), have an established role in the treatment of non-small cell lung cancer (NCSLC). Importantly, clinical response is correlated with the presence of certain EGFR mutations, primarily exon 19 deletions and the L858R substitution, hereafter referred to as EGFR-mutant (Lynch 2004, Paez 2004, Mok 2009). For EGFR mutant NSCLC gefitinib or erlotinib is currently used as the first-line therapy world-wide. However, despite the dramatic responses to such inhibitors, patients ultimately progress. In 50-60% of these cases, a secondary point mutation in EGFR occurs resulting in a threonine-to-methionine amino acid change at position 790 of EGFR (T790M) causing resistance to gefitinib or erlotinib (Kobayashi 2005, Kosaka 2006). Third generation (i.e. irreversible; WT EGFR sparing; with relatively equal potency for activating EGFR mutations L858R, ex19del and acquired T790M) EGFR inhibitors are beginning to enter clinical development and are showing significant initial promise (e.g., CO-1686: 67% (6/9) (PRs) in T790M+ NSCLC patients (WCLC 2013), AZD9291: 50% (9/18) PRs in 18 T790M+ NSCLC patients (WCLC 2013). However, it is likely that even third generation EGFR inhibitors may not be sufficient to achieve long-term disease control.

In human malignant disease, the cMet pathway is one of the most frequently dysregulated pathways. Increased activity of the cMet kinase triggers a highly diverse set of signaling cascades, resulting in pleiotropic effects on tumor cells. cMet mutations have been identified in primary tumors as well as metastatic lesions of several other cancers, including gastric, head and neck, liver, ovarian, non-small cell lung and thyroid cancers (Liu 2008, Lorenzato et al 2002). Among them, splicing mutations deleting the juxtamembrane domain of the exon 14 region was identified in primary resected non-small cell lung cancer (Onozato 2009), and was also shown to be functionally activating through stabilizing and delaying the internalization of the receptor (Kong-Beltran 2006). The existence of such mutations has been confirmed from the latest TCGA (The Cancer Genome Atlas) data, which suggested 4.3% cMet exon 14 skipping mutations in 230 NSCLC adenocarcinoma samples (cbioportal.org/public-portal/, TCGA publication, Nature, in press for 2014). Using various biochemical, genetic and pharmaceutical approaches, specific downregulation of HGF or cMet expression or inhibition of cMet kinase activity in HGF/cMet driven tumor cells was demonstrated to significantly decrease cell proliferation, survival, migration and invasion *in vitro*, and reduce tumorigenic

and metastatic potential *in vivo* (Buchanan 2009, Burgess 2006, Tomioka 2001, Zou 2007). Despite these efforts, there are no cMet inhibitors or antagonists approved for the treatment of cancer. Currently, several cMet kinase inhibitors are being evaluated in clinical trials (Comoglio 2008, Liu 2008). Despite promising early data, it is likely that cMet inhibitors as single agents will not be sufficient and thus, combination with other therapies needs to be pursued early.

In addition to its role within tumor cells, cMet signaling also plays a role in immune cells. Specifically, HGF/cMet signaling in monocytes has been demonstrated to shift their differentiation toward regulatory dendritic cells, which in turn inhibit T cell activation (Rutella 2006). Therefore, inhibition of cMet in monocytes may result in enhanced anti-tumor T cell responses.

Cancer immunotherapy relies on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.(Jemal et al 2011, Pardoll et al 2007, Zitvogel et al 2006, Dunn et al 2002) Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR) (Jemal et al 2011), Zitvogel et al 2006, Dunn et al 2002). Collectively, these signals govern the balance between T-cell activation and tolerance. PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.29. PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-g(IFN-g) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes (Sharpe et al 2007). These results suggest that the PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

In vitro, Nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that Nivolumab augmented IFN-g secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) (Wolchok et al 2009). Several anti-PD1 compounds have already entered the clinic with

[redacted]

promising efficacy to date in lung cancer. In a Phase Ib (n=122) nonrandomized trial targeting pretreated advanced NSCLC patients, Nivolumab showed ORR=16.1%; mOS=9.6mo; 1yr OS=43%, and a 2yr OS=32% While in a chemotherapy naïve setting, Nivolumab in a Phase Ib showed mPFS 36.1weeks and 1yr OS=75%. Furthermore, Nivolumab has been combined safely with both cytotoxic platinum doublets at 5 or 10mg/kg as well as with erlotinib 150mg po qd without DLTs in safety determining cohorts (Getting et al 2014, Antonia et al 2014).

Despite these advancements in treatment, lung cancer remains a significant medical need. Both targeted therapies and immunotherapies show promise. This study is designed to test the hypothesis that a combined small molecule targeted-immunotherapy approach can provide synergistic benefit.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of EGF816

EGF816 is a targeted covalent irreversible EGFR inhibitor that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M), while sparing WT EGFR. EGF816 has shown significant efficacy in EGFR mutant (L858R, ex19del and T790M) cancer models (*in vitro* and *in vivo*) with no indication of WT EGFR inhibition at efficacious concentrations.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Non-clinical pharmacokinetics and metabolism

EGF816 exhibited: moderate plasma clearance, a large volume of distribution and a short terminal half-life (~3 h) in rodents; a high clearance, a high volume of distribution and a relatively long terminal half-life (~13 h) in the dog. EGF816 showed high plasma protein binding. Following oral administration, EGF816 showed good oral bioavailability (>55%) in, rodent and dog. EGF816 is highly permeable across the Caco2 monolayer system. Given the high solubility of EGF816 observed across the pH range and in simulated intestinal fluid for both fasted and fed state, it is considered a preliminary biopharmaceutics classification system (BCS) class I compound with low food effect risk. EGF816, showed almost complete recovery of radioactivity (97%) in rat. The predominant route of elimination was via fecal excretion with renal excretion a minor pathway. The predominant circulating component in rat plasma was the parent compound. The cross-species metabolism comparison in hepatocytes showed that the N-demethylation pathway was more predominant in human than in dog and rat. The N-demethylated metabolite (LMI258) showed similar pharmacological activity to EGF816 *in vitro*. The exposure of LMI258 was 3-9% and 20-40% of the parent exposure in rat and dog 4-week toxicology studies, respectively. EGF816 is primarily metabolized by CYP3A4. EGF816 showed weak to moderate inhibition of CYP2D6 (Ki 3.3 µM, unbound) and CYP2C8 (IC_{50} ~11 µM, unbound) whereas metabolite LMI258 showed relatively strong inhibition of CYP2D6 (Ki 0.41 µM) and weak inhibition of CYP3A4 (IC_{50} 12 µM) *in vitro*. EGF816 and LMI258 may increase the exposure of the substrates of these CYP isoforms if sufficiently high concentrations are reached in the clinic. EGF816 is a p-glycoprotein (P-gp) substrate with a Km value of 5.0

[redacted]

to 16 µM, and an inhibitor of breast cancer resistance protein (BCRP) with an estimated IC_{50} value of 4.0 µM.

For more information please refer to the current [EGF816 IB].

1.2.1.1.2 Pharmacology and toxicology

Non-clinical pharmacology

EGF816 is a potent third generation, irreversible EGFR mutant-selective inhibitor. It covalently links to Cys797 at ATP site of EGFR. In cell-based target modulation assays, EGF816 inhibits both oncogenic (L858R, ex19del) and TKI-resistance (L858R/T790M) lines with single digit nM potency and demonstrates good selectivity (~40-60 fold vs. the least active mutant line) over WT-EGFR cell lines. The potency and WT-selectivity of EGF816 was further confirmed in a receptor occupancy study using ^{14}C-labeled EGF816. Profiling against several large panels of kinases indicates that EGF816 is highly selective. The confirmed off-target activities are mostly on kinases containing a similarly located cysteine as Cys797 in EGFR. EGF816 demonstrated strong tumor regressions in several EGFR activating and resistant tumor models *in vivo*. These include HCC827 (ex19del), H3255 (L858R) and H1975 (L858R; T790M) that are representative of the relevant clinical settings. In all of the models EGF816 inhibited tumor growth in a dose-dependent manner and achieved regressions of established tumors at well tolerated doses. The HCC827 (ex19del activating mutation) mouse xenograft model was very sensitive to EGF816. Even at the lowest tested daily dose of 3 mg/kg, significant tumor regression was achieved. The effect was comparable to erlotinib at 60 mg/kg, a clinically relevant dose, which gave free plasma exposure similar to that observed at clinical efficacious dose. At doses of 10 mg/kg q.d. or above, EGF816 showed maximum regression similar to erlotinib at its maximum tolerated dose (MTD) of 120 mg/kg. EGF816 was very well tolerated, with no body weight loss observed up to 100 mg/kg, while erlotinib at 120 mg/kg showed significant body weight loss (~10%). In the H3255 (L858R) mouse xenograft model, EGF816 was tested at 30 mg/kg and demonstrated strong tumor regression with no effect on body weight compared to vehicle. In the H1975 (L858R/T790M) mouse and rat xenograft models, significant tumor regression was achieved at doses ≥ 30 mg/kg. Importantly, EGF816 demonstrated much improved tolerability with superior efficacy as compared to second-generation irreversible pan-EGFR inhibitor afatinib. Dose-dependent inhibition of pEGFR and its down-stream pharmacodynamics (PD) markers were observed following single oral dose of EGF816 at several dose levels. Sustained inhibition of pEGFR relative to plasma PK was evident in either model, and is consistent with the irreversible binding mechanism of action. Targeted inhibition of WT EGFR in cells also inhibits dual specificity phosphatase 6 (DUSP6) (Vecchione et al 2011). In an effort to compare the *in vivo* WT EGFR selectivity of EGF816 and afatinib, the DUSP6 gene expression was measured in the skin of treated animals. While afatinib caused significant DUSP6 inhibition, EGF816 had no effect at the efficacious doses.

For more information please refer to the current [EGF816 IB].

Toxicology

A series of preclinical toxicology studies were completed to support human clinical trials with EGF816, including safety pharmacology studies, genetic toxicology studies, general toxicology

[redacted]

studies, and photosensitization assessment. A 4-week GLP study in rats and a 4-week GLP study in beagle dogs were performed. Target organs in the rat included skin/eyelids (inflammation around hair follicles and in epidermis), lungs (foamy macrophages-phospholipidosis), lymphoid organs (cell depletion), vagina (atrophy of epithelium), uterus (atrophy of endometrium), anal (sebaceous) glands (inflammation). The severely toxic dose to 10% of animals (STD10) was 75 mg/kg/day. Target organs in the dog included cornea (epithelial thinning), and various glands throughout the organ system (atrophy). The highest non-severely toxic dose (HNSTD) was determined to be 20 mg/kg/day.

EGF816 showed a potential for phototoxicity in the 3T3 NRU *in vitro* assay. The Ames assay for EGF816 indicated that it was not a potential mutagen and the chromosomal aberration assay in human peripheral blood lymphocytes did not indicate the potential to cause chromosomal aberrations. An *in vivo* evaluation of the bone marrow for the presence of micronuclei was negative in rats. The IC50 for the hERG potassium channel is 6 μM.

For more information please refer to the current [EGF816 IB].

1.2.1.2 Clinical experience

CEGF816X2101 is the first-in-human Phase I/II study of single-agent oral EGF816. As of the data cut-off date (18-Dec-2015), in this study 148 patients have been treated with EGF816 capsules or tablets at seven dose levels: 75 mg q.d. (N=7), 100 mg q.d. (N=29), 150 mg q.d. (N=64), 200 mg q.d. (N=8), 225 mg q.d. (N=24), 300 mg q.d. (N=5) and 350 mg q.d. (N=11). Eighty-four patients (56.8%) were still receiving treatment and 64 patients (43.2%) had discontinued treatment. Of these 64 patients, 53 (35.8%) discontinued treatment due to progressive disease, three (2.0%) discontinued treatment due to adverse events (AEs), and 3 (2.0%) discontinued treatment due to death. Of the three patients who discontinued treatment due to AE, one patient at the 350 mg q.d. reported Grade 3 maculopapular rash, one patient at the 150 mg daily dose reported Grade 3 interstitial lung disease, and one patient at the 300 mg daily dose reported Grade 3 pulmonary edema. Of the three patients who discontinued treatment due to death, one patient died due to sepsis (considered not related to study treatment), one patient died due to hepatitis B virus (HBV) reactivation (considered related to study treatment), and one patient died due to pneumonia (considered not related to study treatment).

As of 18-Dec-2015, dose-limiting toxicities (DLT) were reported in five patients: one patient at the dose level of 150 mg capsule reported Grade 3 maculopapular rash that resulted in temporary treatment interruption, one patient at the dose level of 225 mg capsule reported Grade 3 maculopapular rash that resulted in temporary treatment interruption, one patient at the dose level of 350 mg capsule reported Grade 3 acute kidney failure and Grade 3 maculopapular rash that resulted in temporary treatment interruption, one patient at the dose level of 350 mg capsule reported Grade 3 maculopapular rash that resulted in permanent discontinuation of treatment, and one patient at the dose level of 350 mg capsule reported Grade 3 enteritis and Grade 3 dehydration that resulted in temporary treatment interruption.

The maximum tolerated dose (MTD) has not been determined for EGF816 as a single agent.

As of the data cutoff date of 18-Dec-2015, 142 patients (95.9%) who were treated with EGF816 capsules or tablets experienced at least one AE of any grade, regardless of relationship to the study drug. The most frequent AEs (all CTCAE grades, >10% of patients) regardless of study

[redacted]

drug relationship at the seven dose levels were rash (group term) (56.1%), diarrhea (41.9%), maculopapular rash, pruritus (36.5%), fatigue (27.0%), stomatitis (27.0%), dry skin (24.3%), nausea (23.6%), cough (20.9%), decreased appetite (20.3%), vomiting (14.9%), constipation (14.2%), headache (12.8%), anemia (12.2%), paronychia (11.5%), pyrexia (11.5%), dyspnea (10.8%), edema peripheral (10.8%), back pain (10.1%), and upper respiratory tract infection (10.1%).

Seventy (47.3%) patients who were treated with EGF816 capsules or tablets at any dose experienced Grade 3 or Grade 4 AEs regardless of relationship to the study drug. Grade 3/4 AEs occurring in ≥ 2% of patients were rash (grouped term) (15.5%), anemia (5.4%), pneumonia (5.4%), diarrhea (4.7%), fatigue (2.7%), dyspnea (2.7%), urticaria (2.7%), hypertension (2.7%), stomatitis (2.0%), decreased appetite (2.0%), hyperuricemia (2.0%), and seizure (2.0%).

As of the data cutoff date (18-Dec-2015), SAEs, regardless of study drug relationship, were reported in 48 patients (32.4%) who received at least one dose of single agent EGF816 capsules or tablets. Of these 48 patients, 15 experienced SAEs that were suspected to be related to study drug or study procedures: one patient at the 350 mg capsule daily dose was reported to have Grade 3 acute kidney injury that resulted in temporary drug interruption, one patient at the 350 mg capsule daily dose was reported to have Grade 3 dehydration and enteritis that resulted in temporary drug interruption, one patient at the 225 mg capsule daily dose was reported to have Grade 3 hepatitis B reactivation and Grade 3 hepatic failure that resulted in permanent treatment discontinuation and death, one patient at the 225 mg capsule daily dose was reported to have Grade 3 purpura that resulted in temporary drug interruption, one patient at the 225 mg capsule daily dose was reported to have Grade 3 hepatitis B reactivation that resulted in temporary drug interruption, one patient at the 225 mg capsule daily dose was reported to have Grade 3 maculopapular rash that resulted in temporary drug interruption, one patient at the 225 mg capsule daily dose was reported to have Grade 3 diarrhea that resulted in temporary drug interruption, two patients at the 150 mg capsule daily dose reported Grade 2 dyspnea that resulted in no action taken with study drug, one patient at the 150 mg capsule daily dose was reported to have Grade 1 acute renal failure that resulted in temporary drug interruption, one patient at the 150 mg capsule daily dose reported Grade 2 diarrhea that resulted in temporary drug interruption, one patient at the 150 mg capsule daily dose was reported to have Grade 3 interstitial lung disease that resulted in temporary drug interruption, one patient at the 150 mg capsule daily dose was reported to have Grade 3 pneumothorax that was related to a study-associated procedure that occurred after the patient had discontinued study drug, one patient at the 150 mg tablet daily dose was reported to have Grade 3 diarrhea that resulted in temporary drug interruption, and one patient at the 150 mg tablet daily dose was reported to have Grade 3 upper gastrointestinal hemorrhage that resulted in temporary drug interruption and was reported to have Grade 3 anemia (the SAEs of gastrointestinal hemorrhage and anemia were updated to not suspected related to study treatment in the safety database, but have not been updated in the clinical database).

As of 18-Dec-2015, the outcome of SAEs suspected to be related to study treatment was recovered or recovering in 12 of 15 patients. One patient died due to hepatic failure secondary to HBV reactivation, one patient was reported as not recovered from Grade 3 maculopapular rash, and one patient was reported as not recovered from Grade 3 anemia.

[redacted]

As of 18-Dec-2015, 2 SAEs of HBV reactivation have been reported in 2 patients participating in the CEGF816X2101 study. One case had a fatal outcome, and the second case was considered medically significant. The fatal case involved a patient who received EGF816 at 225 mg q.d., had a history of HBV infection and was not on antiviral treatment at study entry. The patient developed HBV reactivation during the study and died due to hepatic failure despite initiation of antiviral treatment after HBV reactivation had been confirmed. The second patient also received EGF816 at 225 mg q.d., had a history of HBV and was not on antiviral treatment at the time of joining the study, HBV reactivation was detected after the patient had been on study for approximately 10 weeks. Antiviral treatment was immediately initiated, EGF816 was interrupted and the HBV infection was brought under control. The patient later resumed EGF816 at the same dose of 225 mg q.d. while continuing on antiviral medication. The viral reactivation in these two patients was likely due to immunosuppression related to EGF816. Reactivation of HBV and hepatitis C virus (HCV) has been reported with anticancer therapies that suppress the immune system.

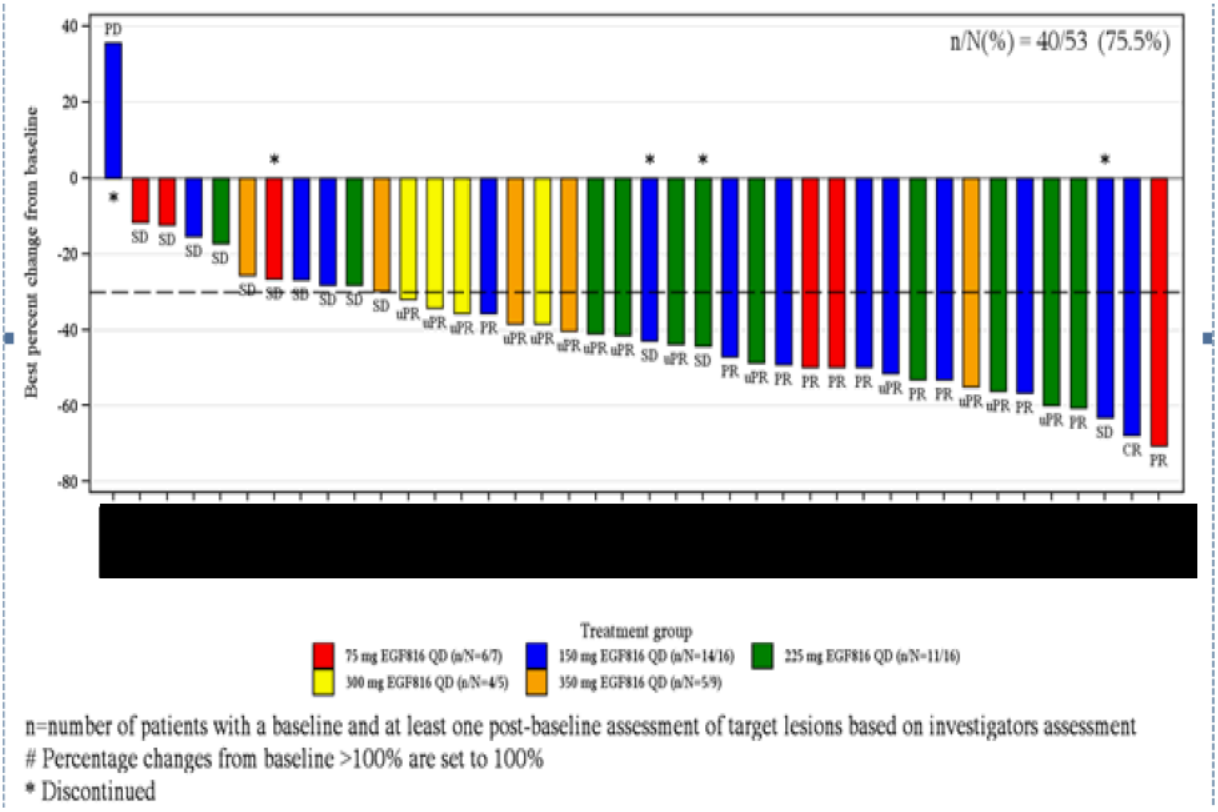
It should be noted that the maculopapular rash associated with EGF816 treatment appeared to be different from the typical EGFR TKI-related rash (e.g., acneiform rash). Its onset was generally in the first 2-3 weeks of study treatment however it could be sporadic. The rash typically started on the trunk, spread out to the extremities, and in general spared the palms and soles. EGF816-associated rash was well managed with dose interruption and/or steroid and antihistamine treatments. In most cases, the rash resolved completely or almost completely within 1 week with drug interruption, and patients were able to restart study treatment, at the same dose or a reduced dose, without recurrence of the maculopapular rash

As of 02-February-2015, preliminary efficacy results showed an overall response rate (ORR) of 59.5% by Investigator assessment in 25 (11 confirmed and 14 awaiting confirmation) out of 42 evaluable patients treated at all dose levels. Note: evaluable patients include those who were ongoing and had at least one post-baseline tumor assessment or who discontinued study treatment as of the data cut-off date. The antitumor activity of EGF816 is in line with the antitumor activity observed with other 3rd-generation EGFR TKIs including AZD9291and CO-1686. Refer to Figure 1-1.

Please refer to the current Investigator's Brochure [EGF816 IB] for more details.

[redacted]

Figure 1-1 Best percentage change from baseline in sum of diameters of target lesions as per investigator by treatment (Capsule) – Full analysis set



n=number of patients with a baseline and at least one post-baseline assessment of target lesions based on investigators assessment
# Percentage changes from baseline >100% are set to 100%
* Discontinued

1.2.2 Overview of INC280

The chemical name for INC280 is 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl) imidazo[1,2b][1,2,4]triazin-2-yl)benzamide dihydrochloride. INC280 is a small adenosine triphosphate (ATP) competitive, reversible inhibitor of the cMet receptor tyrosine kinase.

Please refer to the current INC280 Investigator's Brochure for more detailed information

1.2.2.1 Non-clinical experience

1.2.2.1.1 Pharmacology summary

The pharmacokinetic/pharmacodynamic (PK/PD) relationship of INC280 was characterized in tumor-bearing mice. These experiments probed the potential of INC280 to inhibit phosphorylation of cMet, as assessed by phospho-cMet levels in tumors using immunohistochemical or ELISA-based methods. In cMet/hepatocyte growth factor (HGF)-driven xenograft mouse tumor models, oral dosing of INC280 demonstrated significant in vivo activity in blocking cMet phosphorylation. Tumor regression at well-tolerated doses was observed in cMet amplified models (gastric cancer model GTL-16 and liver cancer model HCC-LM3) as well as cMet/HGF co-expressing models, where cMet is activated in an autocrine fashion (e.g. glioblastoma model U-87 MG). For more information, refer to the current [INC280 IB].

1.2.2.1.2 Non clinical drug metabolism and pharmacokinetics summary

INC280 was absorbed rapidly, and the absolute oral bioavailability (F%) was low to moderate (24-66%) in rats, dogs and monkeys. Single and multiple dose toxicokinetic studies in rats and monkeys showed that plasma INC280 maximum concentration (Cmax) and area under the concentration-time curve (AUC) increased with dose, although not always dose-proportional. INC280 plasma protein binding was moderate to high across species, and was 93.3% in humans. The in vitro blood-to-plasma ratio in humans was 1.7. INC280 was widely and rapidly distributed to all tissues following a single oral dose in rats. Melanin rich tissues, including eye choroid, uveal track and meibomium glands, appeared to have prolonged retention of the drug related materials. INC280 can penetrate across the blood-brain barrier in the rat with a brain-to-blood ratio of approximately 0.1. In the rat, INC280 was mainly eliminated through biliary excretion via metabolism. INC280 is predominantly metabolized by cytochromes P450 (CYP) 3A4 in human hepatic microsomes. INC280 showed inhibitory potency in vitro against CYP1A2, 2C8, 2C9, 2C19 and 3A4/5. INC280 also displayed inhibition of multidrug resistant 1/Permeability glycoprotein (P-gp), MXR/breast cancer resistant protein (BCRP), organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 mediated substrate efflux or uptake. Therefore, at clinical relevant doses, potential drug-drug interactions are possible due to inhibition of CYP1A2, 2C8, 2C9, 2C19 and 3A4/5 metabolic enzymes, and/or due to inhibition of P-gp, BCRP, and OATP1B1/1B3 transporters.

For more information, refer to current [INC280 IB].

1.2.2.1.3 Non clinical toxicology summary

A series of preclinical toxicology studies were completed to support human clinical trials with INC280, including safety pharmacology studies, genetic toxicology studies, general toxicology studies (single-and repeat-dose studies) in the mouse, rat, and monkey (in rats and monkeys up to 13-weeks in duration), embryofetal developmental toxicity studies, and photosensitization assessment. Safety pharmacology studies with INC280 indicated that INC280 had no significant effects on vital organ functions. Repeat dose toxicity studies conducted revealed the following target organs or systems: kidneys, pancreas, central nervous system (CNS), and potentially liver.

INC280 is not genotoxic. Studies on embryo-fetal development in rats and rabbits indicated that INC280 is teratogenic to both species, and the teratogenicity is consistent with the mechanism of action by cMet inhibition. INC280 should be considered potentially teratogenic to humans.

Additionally, INC280 has shown photosensitization potential in in vitro and in vivo assays.

For more information, refer to the current INC280 Investigator's Brochure [INC280 IB].

1.2.2.2 Clinical experience

1.2.2.2.1 Clinical safety

As of 28-Sep-2017, a total of 1109 cancer patients and 158 non-cancer subjects have received INC280. A total of 622 patients with solid tumors have been treated with INC280 as a single agent, and 487 patients have been treated with INC280 in combination therapies. Treatment was with either the capsule formulation or tablets or both. Twenty-one clinical studies are

[redacted]

currently ongoing with INC280. A total of 19 patients have experienced 25 DLTs: 6 patients in single agent studies and 12 in combination studies. For more information, please refer to the current INC280 [Investigator's Brochure].

Overall, the majority of the reported adverse events (AEs) are mild or moderate in severity. The most frequent AEs suspected to be related to INC280 of any grade reported in the largest single agent trial [CINC280A2201] (220 patients) were edema peripheral (77 patients, [35.0%]), nausea (69 patients, [31.4%]), vomiting (40 patients, [18.2%]), blood creatinine increased (39 patients, [17.7%]), and fatigue (34 patients, [15.5%]), majority Grade 1/2. The most frequently occurring Grade 3/4 AEs suspected to be related to INC280 as a single agent included edema peripheral and lipase increased (each in 9 patients, [4.1%]), fatigue (8 patients, [3.6%]), alanine aminotransferase increased (7 patients, [3.2%]), aspartate aminotransferase, hypophosphataemia, nausea and vomiting (each in 3 patients, [1.4%]).

Caution is recommended when INC280 is administered in combination with other anticancer drugs with known risk of hepatotoxicity. One case of liver function test abnormal meeting Hy's Law criteria for hepatotoxicity (PHHO2015CN003025) has been reported for a patient enrolled in the NSCLC combination study with gefitinib [CINC280X2202]. The event could not be attributed solely to either drug alone or to the combination. The patient experienced concurrent elevations of total bilirubin (TBIL) >2×ULN and ALT/AST >3×ULN with ALKP <2×ULN. The patient permanently discontinued both study drugs. Liver function tests improved after treatment discontinuation.

As of the IB cut-off of 28-Sep-2017, one SAE ([redacted]) of interstitial lung disease (ILD) has been reported from INC280 single agent study [CINC280A2201]. A [redacted]-year-old [redacted] patient with prior chemo-radiotherapy developed interstitial lung disease (Grade 3) 57 days after starting treatment with INC280. The investigator assessed the event ILD as related to both INC280 treatment and recent thoracic radiotherapy. Overall, from the single agent study [CINC280A2201] six non-serious cases were reported, of which two cases were suspected by the investigator (outcome: both Grade 2 events and completely recovered) and one Grade 3 SAE ([redacted]; fatal outcome; case described above) have been reported.

Nine ILD/pneumonitis cases were reported in INC280 combination studies with EGFR TKIs (erlotinib [n=1, fatal outcome], gefitinib [n=2, both complete recovery], EGF816 [n=6, four complete recovery, one resolving, and one fatal].

While the risk of pulmonary toxicity/interstitial lung disease (ILD) is a well established class effect for the EGFR TKIs, a casual role of the INC280 to events of pneumonitis cannot be elucidated at the current time.

Investigators are advised to carefully monitor patients receiving INC280 for signs and symptoms of pneumonitis.

The maximum tolerated dose (MTD) for INC280 capsules or tablets as single agent was not reached. The RP2D for INC280 as a single agent has been determined to be 600 mg BID in capsule formulation and 400 mg BID in tablet formulation.

For more information, refer to the current INC280 Investigator's Brochure [INC280 IB].

[redacted]

1.2.2.2.2 Clinical pharmacokinetics

As of 28-Sep-2016, INC280 (capsule and tablet) single agent steady state pharmacokinetic (PK) data are available from five clinical studies ([CINC280X2101T], [CINC280X2102], [CINC280X1101] [CINC280A2201] and [CINC280X2201]), and from four combination studies, INC280 plus gefitinib ([CINC280X2202]), INC280 plus cetuximab ([CINC280X2104]), INC280 plus EGF816 ([CINC280X2105C]) and INC280 plus BKM120 (buparlisib) ([CINC280X2204]) After oral administration, INC280 was rapidly absorbed with the median time to reach maximum drug concentration (Tmax) ranging from 1 to 2 hours for tablets and from 1 to 4 hours for capsules. The elimination half-life estimated from [CINC280X1101] ranged from 3.5 to 6.3 hours across the cohorts. Accumulation in INC280 exposure following repeated administration of 400 mg BID tablets is low, with geometric mean accumulation ratio of 1.4-fold in the single agent [CINC280A2201] study. Steady state INC280 exposure is expected to be reached by the third day of consecutive BID dosing. The mean plasma exposures (Cmax and AUC) for INC280 generally increased with dose up to 600 mg QD and 600 mg BID administration with capsule formulation. The mean plasma exposure increase is roughly dose proportional for INC280 tablet from 200 to 400 mg BID.

A relative bioavailability study, [CINC280X2103], was conducted to compare the INC280 tablet to INC280 capsule. The outcome of this study showed that tablets provided higher systemic exposures (Cmax and AUC) and lower inter-subject variability following a single oral administration of 600 mg INC280 in healthy subjects. Tablet PK data are available in cancer patients at different doses (150 mg to 400 mg BID) in various INC280 studies. In the study [CINC280X2102], the INC280 MF tablet at 400 mg BID (N=8) provided comparable mean AUC0-12h,ss (1. 05-fold) and slightly higher Cmax,ss (1. 44-fold) compared with the INC280 capsule at 600 mg BID (RP2D, N=45) in the limited subjects tested. In the ongoing phase 2 [CINC280A2201] study with FMI tablet, the exposures (both Cmax and AUC) were comparable to what was observed in [CINC280X2102] study at 400 mg BID. Based on the tablet PK and safety data from these studies, the dosage of INC280 at 400 mg BID in tablet form has been declared as the RP2D for the single agent studies.

A study to evaluate the effect of INC280 on the PK of CYP3A4 substrate (midazolam) and CYP1A2 substrate (caffeine) in patients with MET dysregulated solid tumors was completed [INC280A2103]. Multiple doses of INC280 tablets at 400 mg BID did not lead to a clinically significant increase of CYP3A4 substrate (midazolam) exposure. However, AUC of CYP1A2 substrate (caffeine) increased by 135%.

A study to evaluate the effect of INC280 on the PK of Pgp substrate (digoxin) and BCRP substrate (rosuvastatin) in patients with MET dysregulated solid tumors was completed [INC280A2105]. Multiple doses of INC280 tablets at 400 mg BID led to a 74% increase in digoxin Cmax and a 47% increase in AUC. Rosuvastatin Cmax and AUC increased 204% and 108%, respectively.

A study to evaluate the effect of itraconazole (strong CYP3A4 inhibitor) and rifampicin (strong CYP3A4 inducer) on the single-dose pharmacokinetics of INC280 in healthy subjects was completed [INC280A2102]. When co-administered with itraconazole, INC280 AUC increased by approximately 40%. There was no change in Cmax. When co-administered with rifampicin, INC280 AUC and Cmax decreased by approximately 66% and 56%, respectively.

[redacted]

Preliminary pharmacokinetics data from the ongoing study [CINC280A2108], in which INC280 tablet was administered with food in cancer patients, showed no food effect of high fat meal on INC280 exposure. Thus, INC280 can be taken with or without food.

INC280 displayed pH-dependent solubility in vitro. A study to evaluate the effect of a long acting proton pump inhibitor on the PK of a single dose of INC280 tablet was completed in healthy volunteers [CINC280A2101]. Daily treatment with 20 mg rabeprazole for 4 days resulted in a modest reduction in the extent of INC280 absorption with a 25.2% decrease in AUCinf and a 37.5% decrease in Cmax. The effect of food on the rate and extent of INC280 exposure was assessed after a single oral dose administration of 600 mg INC280 tablet in healthy subjects ([CINC280X2107]). Compared to fasting conditions, a low fat meal increased AUCinf and Cmax by 1.20- and 1.11-fold, respectively; and a high fat meal increased AUCinf and Cmax by 1.46- and 1.15-fold, respectively. Preliminary pharmacokinetics data from the ongoing study [CINC280A2108] which INC280 tablet was administered with food in cancer patients, showed no positive food effect of high fat meal on INC280 exposure. While the data on the concurrent use of PPI and food have to be considered preliminary as they have been generated in a small cohort of patients of the study [CINC280A2108], the decrease in exposure imposes caution on the use of PPI when INC280 is taken without regard to food.

INC280 does not show a risk of QT prolongation. Preliminary analysis on 110 patients in study INC280A2201 showed that no patients had new post-baseline QTcF values greater than 500 ms. Changes from baseline (ΔQTcF) greater than 60 ms were not observed and changes greater than 30 ms and below 60 ms were observed in 4 patients (4/110, 3.6%). The observed mean QTcF changes from baseline around Tmax (2 hours post-dose) were 5.21 ms on Cycle 1 Day 1 and -0.54 ms on Cycle 1 Day 15. Based on the PK/QT analysis, the estimated mean ΔQTcF (upper one-sided 95% CI) at mean steady state INC280 concentration 2 hours post-dose (4584 ng/mL) was 0.11 ms (1.85 ms) at the recommended phase 2 dose of 400 mg BID with tablets. The upper one-sided 95% CIs for the estimated mean ΔQTcF at clinically relevant INC280 concentrations are below the regulatory threshold of 10 ms.

For more information on the clinical studies and pharmacokinetics of INC280, refer to the current [INC280 IB].

1.2.3 Overview of Nivolumab

Nivolumab is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response.

1.2.3.1 Non-clinical experience

1.2.3.1.1 Non clinical pharmacokinetics, immunogenicity, and toxicity

Nivolumab was well tolerated in a 3-month intravenous (IV) repeat-dose (twice weekly) toxicology studies in monkeys at doses up to 50 mg/kg, with no effect on body weight and no clinical findings. Serum chemistry changes were limited to reversible 28% decrease of T3 in female monkey at 50 mg/kg dose. No T4 and TSH level changes observed. The highest tolerated

[redacted]

dose was 50 mg/kg twice weekly, which is at least 20 times greater than doses that demonstrated antitumor activity in humans (Wang et al 2014)

Pharmacokinetic study after single i.v. administration at 1 and 10 mg/kg in monkey showed that the concentration declined in a multi-phasic manner with Tmax observed within 0.5 hour. The apparent terminal half -life was 124-139 hours at 1 mg/kg and 261 hours at 10 mg/kg. Serum Nivolumab had a relative slow clearance with limited extra vascular distribution as demonstrated by a Vss value consistent with plasma volume.

Anti-Nivolumab antibody response were positive at day 28 at dose 1 and 10 mg/kg is some animals, but no substantial impact on PK and no adverse effects observed (Wang et al 2014)

1.2.3.2 Clinical experience

1.2.3.2.1 Clinical pharmacokinetics

Single dose pharmacokinetics (PK) of nivolumab was evaluated in subjects with multiple tumor types in CA209001, whereas multiple dose PK is being evaluated in subjects in CA209003. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from 350 subjects from CA209001, CA209002, and CA209003.

The pharmacokinetics (PK) of Nivolumab was linear in the range of 0.1 to 10 mg/kg and both elimination and distribution of Nivolumab in the dose range studied appear to be independent of dose while end of infusion and minimum serum concentration (Cmin) after the first dose were approximately dose proportional. No differences in PK were observed across tumor types with every 2 week administration. The mean terminal elimination half-life of Nivolumab determined from a single dose in Nivolumab study is 17 to 25 days which is consistent with half-life of endogenous IgG4, indicating that the elimination mechanism of Nivolumab may be similar to IgG4.

A preliminary PK model was developed by nonlinear mixed effect modeling using data from 350 adult subjects. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights (BW), and, therefore, confirms the appropriateness of this body weight adjustment of Nivolumab dose. The PK of Nivolumab was well characterized by a linear two compartment model with zero-order IV infusion and first-order elimination. Typical CL and Vc estimates are: 0.0104 L/h and 4.56 L, with 52.8% and 29.6% inter-individual variability. Baseline BW, sex, C-reactive protein, albumin, appear to have >20% effect on clearance (CL); BW and sex also appear to have a >20% effect on Vc BW normalized dosing produces relatively constant Nivolumab steady-state exposures across a wide BW range (40 to 150 kg).

1.2.3.2.2 Clinical safety

Please refer to the nivolumab (Opdivo®) prescribing information and the current nivolumab IB for clinical safety information. Nivolumab has been safely combined with both chemotherapy and erlotinib (Antonia et al 2014, Naiyer et al 2014).

On [redacted], Novartis received a serious adverse event report of a Grade 3 rash in a [redacted] year-old patient treated in Group 1 (EGF816 plus nivolumab) of CEGF816X2201C. Despite discontinuation of the study drugs and treatment with IV methylprednisolone and IV

[redacted]

immunoglobulin, the patient's condition deteriorated and became clinically consistent with toxic epidermal necrolysis (TEN), with desquamation occurring over approximately 95% of [redacted] body surface area (BSA). Although the extent of desquamation began to improve while the patient was under treatment [redacted], [redacted] died while an inpatient on [redacted] from complications of this adverse event. A skin biopsy obtained at the time of the patient's presentation with rash on [redacted] was evaluated as consistent with erythema multiforme/Stevens-Johnson Syndrome (SJS). However, the extent of BSA involvement suggested clinical consistency with TEN.

TEN is an expected adverse event associated with the use of nivolumab, described in the nivolumab Investigator Brochure (Table 5.6.1-1, version 14, 30-Jun-2015) and in the Informed Consent Form for study CEGF816X2201C. TEN/SJS has been reported as a rare event occurring in association with nivolumab. As of 03 July 2015, approximately 11,196 subjects have been exposed to nivolumab in clinical trials, and 1,870 patients have been exposed to nivolumab post-marketing. A cumulative search of the Bristol-Myers-Squibb AWARE safety database identified 4 cases from clinical trials, 3 TEN and 1 SJS. The frequency of TEN was 0.027% and of SJS was 0.009%. There were no cases reported from the post-marketing setting as of 03 July 2015. No cases of SJS/TEN have been reported in the EGF816 single agent study (CEGF816X2101), based on the clinical database on 09 December 2015. A search of the Novartis Argus Safety Database for EGF816 similar cases was performed on 03 Dec 2015 using the MedDRA 18.1 System Organ Class (SOC) "skin and subcutaneous tissue disorders". No similar SJS/TEN cases were identified. However, rash is a common side effect of EGF816 and the possibility cannot be excluded that a potential interaction between EGF816 and nivolumab may increase the frequency of TEN, compared to the frequency associated with nivolumab alone.

On December 31, 2015 Novartis received a report of a serious adverse event (SAE) of Grade 3 pneumonitis occurring in a [redacted]-year-old patient treated in Group 1 (EGF816 plus nivolumab) of CEGF816X2201C. The patient, who was a non-insulin-dependent diabetic had initially presented with hyperglycemia and diabetic ketoacidosis (DKA) on [redacted]. Both study drugs were interrupted at that point, with the last dose of nivolumab having been on [redacted] and the last dose of EGF816 on [redacted]. On admission on [redacted], the patient did report shortness of breath, but SpO2 was 98% on room air and a chest radiograph was clear. [redacted] was treated with IV insulin and hydration and [redacted] blood sugars came under control within 48 hours; [redacted] also received empiric ciprofloxacin because sepsis could not be excluded as a trigger for DKA. However, on [redacted] shortness of breath worsened, SpO2 was 88%, temperature was 38 degrees Celcius, and a chest CT revealed bilateral ground glass opacities suggestive of pneumonitis. [redacted] was treated with high-dose IV steroids, anti-microbials including meropenem, azithrocmycin, and oseltamivir, furosemide, and also received a dose of infliximab. Bronchoscopy and bronchoalveolar lavage performed on [redacted] revealed no evidence of micro-organisms. The patient's respiratory condition continued to deteriorate, and on [redacted] the patient died from pneumonitis.

According to the U.S. Prescribing Information for nivolumab, pneumonitis, including interstitial lung disease, was reported in 3.4% (10/287) of patients treated with single-agent nivolumab in a study conducted in patients with metastatic non-squamous NSCLC. Based on

[redacted]

clinical database review as of 19 Jan 2016, in the EGF816 single-agent study (CEGF816X2101) one case of interstitial lung disease and one case of pneumonitis (which was reported as a non-serious adverse event) have been reported in 146 patients treated, and in the EGF816 plus nivolumab arm (Group 1) of CEGF816X2201C, one case of interstitial lung disease (which was reported as a non-serious adverse event) and two cases of pneumonitis, including the one described herein, have been reported in 18 patients treated. No cases of pneumonitis or interstitial lung disease have been reported in 4 patients treated in Group 2 (INC280 plus nivolumab). Based on these data the possibility cannot be excluded that the risk of pneumonitis/interstitial lung disease may be higher with the combination of EGF816 and nivolumab than with either drug alone.

One patient who received combination therapy of INC280 and PDR001 (a PD-1 inhibitor, i.e. the same drug class as Nivolumab) in the Novartis study CPDR001J2201, experienced Grade 1 myocarditis and hepatitis (serious) approximately two months after initiation of therapy. The subject was treated with corticosteroids. At the time of reporting, hepatitis has fully recovered and myocarditis was ongoing.

2 Rationale

2.1 Study rationale and purpose

Currently approved EGFR TKIs are effective in activated EGFR mutant NSCLC (Section 1.1), however nearly all patients develop resistance. cMet positive NSCLC patients progressing on chemotherapy fare prognostically worse than their non-cMet positive counterparts. Inhibition of cMet in cMet positive NSCLC cells may inhibit their growth, while inhibition of cMet in immune cells may enhance anti-tumor immunity. Harnessing the immune system to treat patients with non-small cell lung cancer (NSCLC) represents a novel and exciting new treatment approach. The anti-PD-1 antibody Nivolumab has demonstrated response rates of up to 20% in patients with NSCLC and has been safely combined with several small molecules as well as cytotoxic chemotherapies.

In order to explore the hypothesis that concurrent treatment with an immune checkpoint inhibitor along with a targeted therapy is safe and may result in durable and sustained responses, Nivolumab will be combined with either the third generation EGFR TKI, EGF816, in EGFR T790M NSCLC patients who have developed resistance to EGFR TKI treatment or with the highly selective and potent cMet inhibitor, INC280, in cMet positive (EGFR wild type) patients who progressed on chemotherapy.

2.2 Rationale for the study design

This study is 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 EGFRwt non-small cell lung cancer. This study is designed to target patients with NSCLC progressing on standard of care (e.g., erlotinib or gefitinib for EGFR-mutant NSCLC or platinum doublet chemotherapy for EGFR wt NSCLC).

[redacted]

This study is designed to include a safety monitoring cohort consisting of a minimum of six (6) T790M positive NSCLC patients and a minimum of 6 EGFR wt NSCLC patients. The safety monitoring cohort will be used to assess the safety profiles during the first six weeks and ensure that the observed exposures (PK) of the combinations are in range of those observed for the single agents at efficacious dosages of EGF816 with Nivolumab or of INC280 with Nivolumab. Enrollment of additional patients at the ongoing dose level will be put on hold until the decision for study continuation is made after reviewing the data from the safety monitoring cohort at the end of the six week period. At a joint meeting, Novartis and study investigators will use clinical and laboratory data obtained from the safety monitoring cohort to make an assessment on the safety of the combination dose for study (as per Section 8). Such data review and meeting may take place before the end of the six week period in case of potential safety concerns. If data from the safety monitoring cohort do not support study continuation with the initial doses or accumulating data from this study and/or other ongoing studies with these agents suggest that alternative lower doses should be explored then additional safety monitoring cohorts at alternative lower dose levels may be opened at any point in time following completion of accrual of the prior cohort after discussion and agreement between Novartis and investigators. However, the decision to resume enrollment at a given dose to reach the targeted enrollment in each treatment group, as specified in Section 5.1, must be based on assessment of data at the time when patients in the safety monitoring cohort at this given dose have completed six weeks of treatment or discontinued earlier.

The objectives of the study are to determine if the combination of EGF816 with nivolumab provides a clinically meaningful benefit over single agent EGF816 or single agent nivolumab observed in similar populations in historical and/or ongoing trials, and if the combination of INC280 with nivolumab provides clinically meaningful benefit over the single agent INC280 or single agent nivolumab in similar populations observed in historical and/or ongoing trials.

2.3 Rationale for dose and regimen selection

In this study the selection of dosing regimen of INC280 and EGF816 is based on the currently available preclinical and clinical safety, efficacy, PK and PK/PD information for the investigational agents – EGF816, INC280 and Nivolumab.
Based on currently available non-clinical and clinical data, the provisional dose will be 400 mg bid for INC280 (tablet formulation) and 150 mg qd on a continuous daily dose for EGF816 (capsule formulation). If prior to the first patient being treated on study, the data from ongoing single agent studies that are available support different EGF816 and/or INC280 doses, Novartis and Investigators will meet via teleconference to review the available single agent data for EGF816 and INC280. (Section 4.1 and Section 10).

The dose and schedule of Nivolumab is 3 mg/kg every 2 weeks. This dose and schedule selection is based on results of safety, efficacy, and exposure-response analyses obtained from studies as described above. (Section 1.2.3) This dose and schedule of Nivolumab has been safely combined with other EGFR inhibitors (e.g., erlotinib) at registered doses as well as with other standard of care therapies (e.g., chemotherapies and ipilumumab) (Naiyer et al 2014, Antonia et al 2014).

[redacted]

2.4 Rationale for choice of combination drugs

This study is designed to:

1. explore if the combination of Nivolumab with the EGFR inhibitor, EGF816, will provide sustained clinical benefit to NSCLC patients whose tumors have become resistant to EGFR TKI treatment through acquiring T790M mutation by stimulating the host immune system and inhibiting EGFR T790M; and
2. explore if the combination of Nivolumab with the cMet inhibitor INC280 will provide sustained clinical benefit to NSCLC patients whose tumors are EGFR wt by stimulating the host immune system and inhibiting the cMet pathway in tumors and/or immune cells.

2.5 Rationale for maximum 2-year duration of Nivolumab treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the Nivolumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment.

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of Nivolumab in patients with previously treated advanced solid tumors (including 129 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with non-small cell lung cancer (NSCLC) who discontinued Nivolumab after completing 2 years of treatment, 12 subjects were alive > 5 years and remained progression-free without any subsequent therapy. In this NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years (Brahmer et al 2017). These survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which Nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively) (Felip et al 2017). Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in subjects with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both Pembrolizumab 2 mg/kg (HR 0.72, $p = 0.00017$) and pembrolizumab 10 mg/kg (HR 0.60, $p < 0.00001$) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years (Herbst et al 2016). Keynote-006 was a randomized phase 3 study of pembrolizumab versus ipilimumab in patients with advanced melanoma, which also specified a maximum 2 year duration of pembrolizumab treatment. Of the 556 patients randomized to pembrolizumab, 104 (19%) of them completed 2 years of treatment. With a median follow-up of 9 months after completion of pembrolizumab, the estimated risk of progression or death was 9% in these patients (Robert et al 2017). Another recent analysis in a

[redacted]

melanoma study suggests the majority of patients who discontinue Nivolumab for toxicity maintain disease control in the absence of further treatment (Schadendorf et al 2016).

In conclusion, these data suggest that there is minimal if any benefit derived from continuing checkpoint inhibitor immunotherapy treatment beyond 2 years in advanced tumors. Even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, treatment will be given for a maximum of 2 years from the start of study treatment following the approval of protocol amendment 08.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
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)	
Secondary		Refer to Section 10.5.
To evaluate the preliminary antitumor activity of EGF816 and Nivolumab and of INC280 and Nivolumab	ORR, DCR, other PFS measures, OS	
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	
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	

[redacted]

[redacted]

4 Study design

4.1 Description of 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.

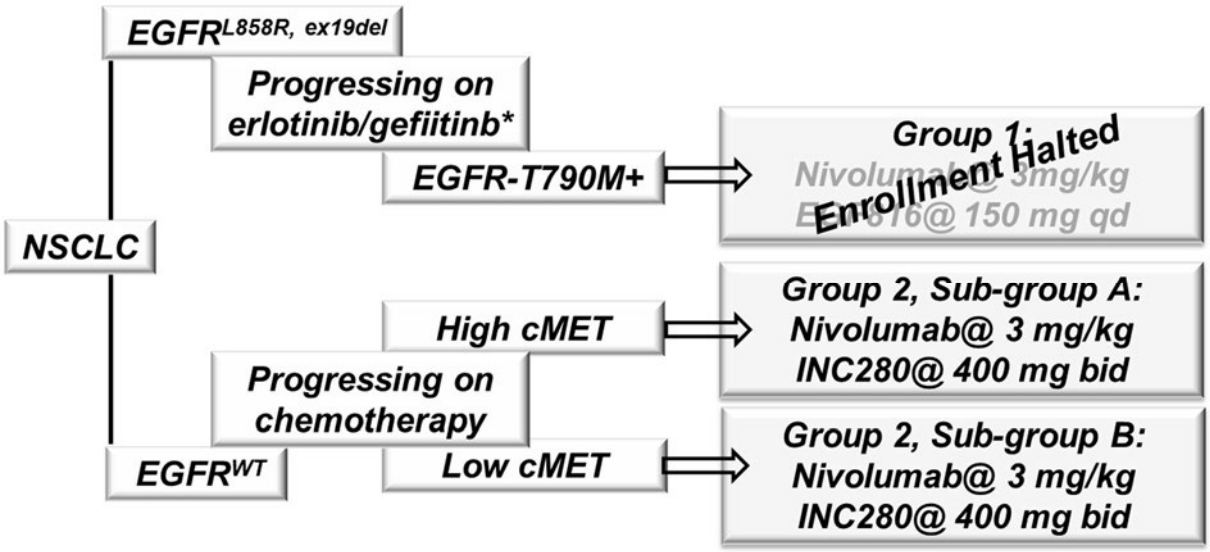
Based on group allocation, patients will be treated as follows:

- 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 4-1 for an overview of the study design

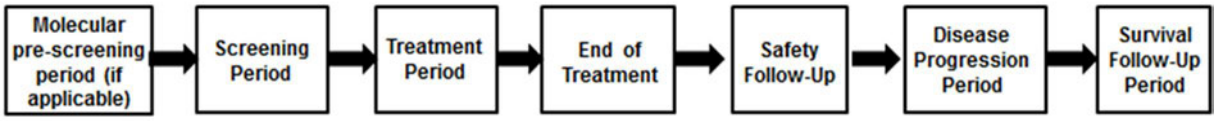
Figure 4-1 Study design



Please refer to Section 5 and Section 7.1 for further details. (*or other approved EGFR TKIs)

[redacted]

Figure 4-2 Study visit flow



At least six patients of each group will constitute a safety monitoring cohort for that group. For each group, patients will be treated with either nivolumab 3mg/kg every two weeks and EGF816 at 150mg qd or with nivolumab at 3mg/kg every two weeks and INC280 400mg bid. As part of the safety monitoring cohort, steady state PK profile for INC280 or EGF816 will be collected on Cycle 1 day 15, and trough samples for nivolumab will be collected on Cycle 1 Day 15.

When patients in the safety monitoring cohort have completed six weeks of treatment or discontinued earlier, Novartis and principal investigators will have a safety assessment meeting to review clinical, PK and laboratory data and decide on the dose for study continuation. Based on emerging data, this meeting may also take place earlier to address potential safety concerns. At this meeting, Novartis and the principal investigators must reach consensus as to whether the current doses in combination do not pose any additional safety concerns over those observed from the single agents. If safety concerns are noted in a given group following review of the data, a decision can be made to evaluate the next 6 patients at a lower dose level of EGF816 or INC280 with Nivolumab at 3mg/kg and repeat a medical review as part of another safety assessment meeting; or to terminate the respective treatment group. Alternatively, if no safety concerns are noted and data from other ongoing studies suggest that a higher dose of EGF816 or INC280 may be more appropriate a decision can be made to evaluate the next 6 patients at a higher dose level of EGF816 or INC280 with Nivolumab at 3mg/kg and repeat a medical review as part of another safety assessment meeting. If applicable in the event that a higher dose is selected as the final dose, individual patients may be considered for treatment at a dose of EGF816 or INC280 that is higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of EGF816 or INC280, he or she must have received the lower dose for at least two cycles of therapy without a toxicity ≥ CTCAE grade 2 that is at least possibly related to the study drug. In addition, if there are no safety concerns but a lower dose is selected as the final dose based on data from other ongoing studies, no additional safety monitoring cohort is needed and enrollment may proceed to reach the planned sample size at the selected lower dose. Patients who were treated at the higher dose of EGF816 or INC280 will remain at that dose if there are no safety concerns at the discretion of the treating investigator after discussion with Novartis. Novartis will prepare and circulate minutes from this meeting to each investigator for comments prior to finalization.

Once a dose is agreed upon after the safety monitoring cohort, enrollment will resume until the planned enrollment target as defined in Section 5.1, has been achieved in each treatment group.

However, if at any time during the study Novartis determines that a lower dose level of EGF816 or INC280 should be explored, enrollment to the ongoing higher dose group may be stopped and Novartis may require the dose of EGF816 or INC280 to be reduced for any ongoing patients.

Detailed information on all patients will be collected and reported (see Section 10 for details).

[redacted]

Molecular pre-screening

All patients must sign the molecular pre-screening consent to allow for the collection, and submission of tumor tissue to a Novartis designated central laboratory for determination and/or confirmation of protocol specific pre-requisite genetic alterations. Refer to Section 7.1 and Section 7.1.1 for further details.

Screening period

The screening period begins once the patient has signed the study informed consent. Patients will be evaluated against study inclusion and exclusion criteria and safety assessments (Table 7-1 and Section 7.1).

Treatment period

The treatment period will begin on Cycle 1 Day 1. The study treatment will be administered during 28-day cycles. Patients will be treated until unacceptable toxicity, progressive disease, treatment discontinuation at the discretion of the investigator, withdrawal of consent, or the patient is transferred to a Novartis roll-over study or an alternative treatment option that can continue to provide study treatment. Of note, eligible patients can only be transferred after the data cut-off for primary analysis.

Following the approval of protocol amendment 08, the maximum treatment duration for Nivolumab cannot exceed 2 years. Patients who have received Nivolumab beyond 2 years will discontinue Nivolumab treatment and continue on EGF816/INC280 alone. Patients who have previously discontinued EGF816/INC280 and have been receiving Nivolumab alone beyond 2 years will discontinue Nivolumab treatment, have an end of treatment visit and continue with the safety and survival follow-up as per Table 7-1b.

Follow up safety assessments

All patients must complete two safety follow-up assessments at 30 (±5) days and 100 (±7) days after last dose. Information relating to anti-neoplastic therapies taken since discontinuation of study treatment and AEs will be collected for 100 days after the last dose of study treatment.

For patients who transfer to a Novartis roll-over study or an alternative treatment option to continue provision of study treatment, an end of treatment visit will be conducted and follow-up for safety, disease progression and survival will not be performed.

Optional Novartis companion sample collection protocol

Patients may have tumor tissue and blood samples collected at baseline and at disease progression to study the mechanisms of drug treatment resistance. For sites that are participating in a Novartis optional companion sample collection protocol studying treatment resistance, the collection of these samples is guided by the companion sample collection protocol and informed consent once approved and open.

4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned for the study. Please refer to Section 10.7 in the protocol. Within each treatment group when patients in the safety monitoring cohort have completed six

[redacted]

weeks of treatment or discontinued earlier, a qualitative review of clinical, PK and laboratory data in a safety assessment meeting will take place (Section 2.2 and Section 4.1).

4.3 Definition of end of the study

End of study will occur after a minimum of 12 months has elapsed since last patient first treatment and when:

- all patients have either discontinued study treatment and have completed 30-day and 100-day safety follow up, or have been transferred to a Novartis roll-over study or alternative treatment option for continued access to study treatment
- the study is terminated early.

Refer to Section 10 for details of timing of the primary analysis and final reporting of data.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Adult patients with histologically or cytologically confirmed advanced and/or metastatic/unresectable NSCLC will be eligible to participate in this study.

The initial allocation of patients in the two groups will be based on EGFR and cMet status.

Group 1: will enroll at least 40 adult patients with advanced, recurrent or metastatic/unresectable EGFRT790M NSCLC progressing on standard of care (e.g., erlotinib, gefitinib or other approved EGFR TKI). As of December 17, 2015 enrollment to Group 1 has been halted.

Group 2: will enroll at least 50 adult patients, including at least 6 patients in the safety monitoring cohort of Group 2. Sub-group A will enroll approximately 20 high cMet and Sub-group B will enroll approximately 30 low cMet patients.

The cMet status will be classified as high or low according to cMet expression assessed by immunohistochemistry (IHC), cMet gene amplification assessed by fluorescence *in situ* hybridization (FISH), and cMet mutation status. Only IHC and FISH will be performed for pre-screening, whereas mutation testing will be performed retrospectively for the purposes of analysis:

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))

[redacted]

- IHC score = 2+ in at least 50% of tumor cells and GCN ≥ 5
- cMet exon 14 activating mutation positive

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)

The investigator or designee must ensure that only patients who meet all the inclusion and none of the exclusion criteria, as defined in Section 5.2 and Section 5.3 are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Written informed consent must be obtained prior to any screening procedures
2. Patients (male or female) ≥ 18 years of age.
3. Presence of at least one measurable lesion according to RECIST v.1.1 as per Appendix 4.
4. ECOG performance status ≤ 2
5. Patients with histologically documented locally advanced, recurrent and/or metastatic NSCLC
6. Tumor tissue for determination and/or confirmation of genetic pre-requisites (i.e., EGFR T790M positivity post progression on EGFR TKI for Group 1; cMet status for Group 2) must be provided for analysis.
7. Group 1 patients
   a. Patients with EGFR T790M NSCLC (adenocarcinoma)
   b. Documented progression of disease according to RECIST v1.1 following primary standard of care (e.g. erlotinib, gefitinib)
8. Group 2 patients
   a. Patients with EGFR wild-type NSCLC as defined in Section 4.1.
   b. Documented progression of disease according to RECIST v1.1 following standard of care (e.g., platinum doublet).

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. For Group1: Patients who have received more than one prior line of EGFR TKI therapy
2. For Group 2: Previous treatment with a cMet inhibitor or HGF-targeting therapy
3. Patients with brain metastases. However, if radiation therapy and/or surgery has been completed and serial evaluation by CT (with contrast enhancement) or MRI over a minimum of one month demonstrates the disease to be stable and if the patient remains asymptomatic, then the patient with brain metastases may be enrolled. Such patients must have no need for treatment with steroids.

[redacted]

4. Patients who require emergent use of systemic steroids, chronic use of prednisone (greater than 10mg or an equivalent steroid dose daily) or emergent surgery and/or radiotherapy.
5. History of allergy or hypersensitivity to Nivolumab components.
6. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures. Any severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for the study.
7. Patients with any known or suspected, current or past history of, autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
8. Patients with a condition requiring chronic systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment start. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

NOTE: Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses >10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

9. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
10. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

Note: All patients will be screened for HBsAg, HBsAb, HBcAb, HC Ab and Hepatitis C RNA. If a patient tests positive for any of the following: HBsAg, HBcAb or HC Ab or Hepatitis C RNA, then the patient should be excluded from the study. If a patient tests positive only for HBsAb, HBV-DNA should be tested and if this test result is positive the patient should be excluded from the study. Patients who test positive only for HBsAb and negative for HBV-DNA, and have a history of Hepatitis B vaccination, are eligible. Please refer to Appendix 6 for further details.

11. Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
12. Patients with significant or uncontrolled cardiovascular disease (e.g., uncontrolled hypertension, peripheral vascular disease, congestive heart failure, cardiac arrhythmia, or acute coronary syndrome) within 6 months of starting study treatment or myocardial infarction within 12 months of starting study treatment.
13. Unable or unwilling to swallow tablets or capsules

[redacted]

14. Unresolved toxicity greater than CTCAE grade 1 from previous anti-cancer therapy or radiotherapy (excluding neurotoxicity, alopecia, ototoxicity, lymphopenia), or incomplete recovery from previous surgery, unless agreed by Novartis and the Principal Investigator (PI) and documented
15. Prior therapy:
    a. Patients who have been treated with prior PD-1 and PD-L1 agents
    b. Patients who previously received agents targeting cMet and/or EGFR T790M. Note: Previous treatment with afatinib may be allowable after discussions between Novartis and Investigator.
    c. Patients who have been treated with chemotherapy or biologic therapy or other investigational agent < 1 week prior to start of study treatment
    d. Patients who have received radiotherapy to a large volume (including whole brain radiotherapy) < 2 weeks prior to starting study drug, and patients who have received radiotherapy to a small volume (including stereotactic radiotherapy to the CNS) < 1 week prior to starting study drug.
    e. Patients who have undergone major surgery < 2 weeks prior to starting study drug or who have not recovered from the surgical procedure

NOTE: exceptions to the above are possible, on a case by case basis, following discussion and mutual agreement between investigator and Novartis.

16. Patients with the following laboratory abnormalities:
    a. Absolute Neutrophil Count (ANC) <1.5 x 10^9/L
    b. Hemoglobin (Hgb) <9 g/dL
    c. Platelets <100 x 10^9/L
    d. Total bilirubin >1.5 x upper limit of normal (ULN). For patients with Gilbert's syndrome total bilirubin >2.5 x upper limit of normal (ULN).
    e. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN
    f. Serum creatinine >1.5 x ULN and/or measured or calculated creatinine clearance < 75% LLN
    g. For patients being screened for Group 2, asymptomatic serum amylase > CTCAE Grade 2 (1.5-2.0 x ULN). Patients with Grade 1 or Grade 2 serum amylase at the beginning of the study must be confirmed to have no signs or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.)
    h. For patients being screened for Group 2: Serum lipase > ULN
17. Patients receiving treatment with medications that are known to be a) strong inhibitors of CYP3A4 (group 1 only) or strong inducers of CYP3A4 (for both Group 1 and Group 2), b) CYP3A4 or CYP1A2 substrates with narrow therapeutic index (for Group 2 only), and which cannot be discontinued for at least 1 week prior to the start of study treatment. Please refer to Appendix 2 for a list of prohibited concomitant medications
18. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test

[redacted]

19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after stopping investigational medication. Highly effective contraception methods include:
    a. Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    c. Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    d. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

NOTE: In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

20. Sexually active males unless they use a condom during intercourse while taking drug and for 31 weeks after the last dose of study treatment. Patients should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
21. For Group 2: impairment of GI function or GI disease that may significantly alter the absorption of INC280 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome)
22. Patients with Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
23. Patients taking concomitant medication(s) with a “Known Risk of Torsades de Pointes” per www.qtdrugs.org that cannot be discontinued or replaced by safe alternative medication.

6 Treatment

6.1 Study treatment

The investigational drugs to be used in this study are EGF816, INC280 and Nivolumab.

[redacted]

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
EGF816	Capsule for oral use	150 mg	Daily
INC280	Tablet for oral use	400 mg	Twice daily
Nivolumab	Solution for infusion	3mg/kg	Every two weeks

Instructions for administration of EGF816 and INC280

EGF816 will be administered orally on a daily schedule (QD) and INC280 will be administered bid. Both will be administered as a flat-fixed dose, not by body weight or surface area.

INC280 or EGF816 can be taken with or without food. The second (evening dose) for INC280 should be taken 12 hours (+/-2 hours) apart from the first morning dose. Patients will self-administer the study medication with a glass of water (approximately 250 mL; 8.5 ounces) at about the same time every day. Patients will consume another glass of water approximately two hours after each dosing. On the days when PK blood samples are to be collected (Section 7.2.3), patients will be instructed to hold their dose of study drugs and the administration of study drugs will be supervised by the study personnel, and the time of the meal before and after the dose need to be recorded on the eCRF.

During the entire duration of treatment with INC280, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, avoid sunbathing or using a sunlamp or tanning bed).

No food effect is anticipated for EGF816. Preliminary pharmacokinetics data from the ongoing study [CINC280A2108], in which INC280 tablet was administered with food in cancer patients, showed no food effect of high fat meal on INC280 exposure. Thus, INC280 can be taken with or without food.

Patients in Group 1 must avoid consumption of grapefruit, grapefruit juice and grapefruit hybrids at least 7 days prior to the first dose of study treatment and during the entire study treatment period due to potential CYP3A interaction. For patients in Group 2, consumption of grapefruit, grapefruit juice and grapefruit hybrids is allowed with caution during the treatment period.

A missed dose is defined as any time point when a patient forgets to take INC280 or EGF816 within 4 hours after the planned time of dosing or if a patient forgets to take his/her dose for that day. In such cases, the dose should be omitted and the patient should continue treatment with the next scheduled dose.

If vomiting occurs, no attempt should be made to replace the vomited dose. If any episodes of vomiting occurred within the first 4 hours of INC280 and EGF816 dosing on post dose PK sampling days, it must be noted in the Adverse Events CRF and the exact time of vomiting should be recorded on the appropriate Dosage Administration Record Case Report Form (eCRF).

[redacted]

Instructions for administration Nivolumab

Patients should receive Nivolumab at a dose of 3 mg/kg as a 60-minute IV infusion every 2 weeks, starting Day 1 of Cycle 1 for up to 2 years.

Following the approval of protocol amendment 08, patients who have received Nivolumab beyond 2 years will discontinue Nivolumab treatment and continue on EGF816/INC280 alone. Patients who have previously discontinued EGF816/INC280 and have been receiving Nivolumab alone, patients will discontinue Nivolumab treatment, have an end of treatment visit and continue with the safety and survival follow-up as per Table 7-1b.Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the patient weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram.

There will be no dose escalations or reductions of Nivolumab allowed. Patients may be dosed no less than 12 days from the previous dose. There are no premedications recommended for Nivolumab on the first cycle.

Patients should be carefully monitored for infusion reactions during Nivolumab administration. If an acute infusion reaction is noted, patients should be managed according to Section 6.2.

Doses of Nivolumab may be interrupted, delayed, or discontinued depending on how well the patient tolerates the treatment.

General instructions

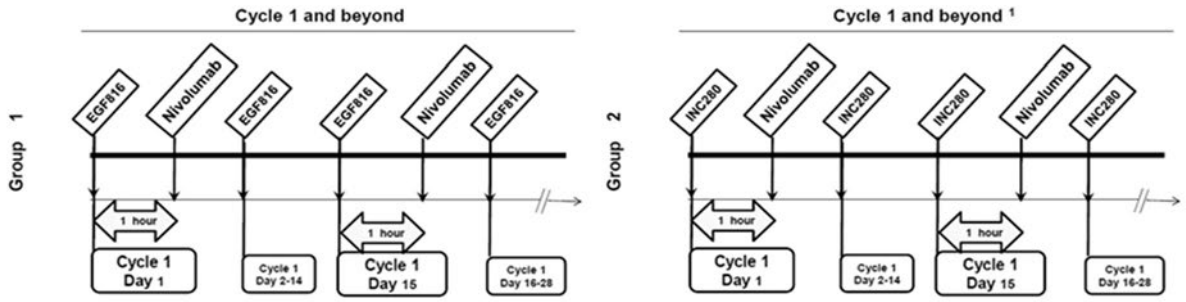
The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes and all missed doses during the study must be recorded on the Dosage Administration Record eCRF. Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at the end of each cycle. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drugs for subsequent dosing.

6.1.2 Sequence of drug administration

EGF816 and INC280 will be administered prior to Nivolumab and its pre-medication (if pre-medication is necessary as per Table 6-7). The sequence will allow consistent time of daily dosing for EGF816 and INC280. A minimum of 1 hour must pass from the time of EGF816 or INC280 (morning dose) administration to the administration of Nivolumab (Figure 6-1).

[redacted]

Figure 6-1 Sequence of drug administration (Group 1: EGF816 and Nivolumab; Group 2: INC280 (AM dose) and Nivolumab)



Note: [1]On days in which Nivolumab is administered, INC280 (morning dose) should be withheld until arrival at the study center. The second (i.e. evening) INC280 dose may be taken outside the site center.

Pre-medications are not required for routine Nivolumab infusions but medications such as anti-histamines (e.g., Benadryl or steroids per Table 6-7) may be administered to treat an existing infusion reaction or as pre-medication for a patient who has previously experienced an infusion reaction at the discretion of the investigator. All pre-medications, with reasons for use, will be recorded in the "Concomitant medications/Significant non-drug therapies" section of the eCRF.

6.1.3 Treatment duration

Patients may continue treatment with the study treatment until patient experiences unacceptable toxicity that precludes any further treatment, disease progression and/or treatment is discontinued at the discretion of the investigator or the patient. Patients may continue Nivolumab treatment for up to 2 years. Refer to Section 7.1.3 and Section 7.1.4.

Following the approval of protocol amendment 08, patients who have received Nivolumab beyond 2 years will discontinue Nivolumab treatment and continue on EGF816/INC280 alone. In patients who have previously discontinued EGF816/INC280 and have been receiving Nivolumab alone, patients will discontinue Nivolumab treatment, have an end of treatment visit and continue with the safety and survival follow-up as per Table 7-1b.

6.2 Dose modification and dose delay

6.2.1 Dose modification and dose interruption for EGF816, INC280 and Nivolumab

Guidelines for dose modifications, dose interruptions and discontinuation of each investigational agent within the combination may be different. In exceptional cases, after discussion with Novartis, patients may be allowed to continue treatment or resume treatment with just one of the investigational drugs. For purposes of this study, the term "discontinue study treatment" will refer to the discontinuation of both investigational agents; while the term "discontinue study drug" will refer specifically to the investigational agent being discussed.

[redacted]

All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of EGF816, or INC280 or Nivolumab for patients receiving Nivolumab-EGF816 or Nivolumab-INC280 combination are listed in Table 6-2.

All interruptions or modifications must be recorded on the Dosage Administration Record CRF.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events for up to 100 days following the last doses of EGF816 or INC280 or Nivolumab – whichever may occur last in any given patient.

Prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events will be as per institutional guidelines.

In case of study treatment interruption, the evaluation visit schedule should still be followed and assessments performed as per Table 7-1 and Table 7-1b.

For either EGF816 or INC280:

Each patient will be allowed two dose reductions to a minimum of 75 mg qd for EGF816 or to a minimum of 200mg bid of INC280. Dose reductions for EGF816 may only be multiples of 25 mg (e.g., to doses of 100 mg or 75 mg) and for INC280 may only be multiples of 100 mg (e.g., to doses of 300 mg or 200 mg bid). If after interruption of treatment and resolution, treatment is resumed at the same dose following the criteria in Table 6-2, and if the same toxicity recurs with the same severity, next treatment re-initiation must resume at a lower dose irrespective of duration of toxicity. In addition, a patient must discontinue treatment if, after treatment is resumed at the minimum dose defined, the toxicity recurs with the same or worse severity unless specified otherwise in Table 6-2. Exceptions can be made on a case by case basis after discussion with Novartis and Investigator.

If a patient requires a dose interruption of either EGF816 or INC280 for > 21 days from the intended day of the next scheduled dose, due to toxicity attributed to EGF816 or INC280, respectively, then the patient must be discontinued from the study treatment unless otherwise specified in Table 6-2.

For Nivolumab:

There will be no dose reductions for Nivolumab.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued Nivolumab dosing may warrant interruption or discontinuation of Nivolumab dosing.

If a patient requires a dose interruption of Nivolumab for > 6 weeks from the intended day of the next scheduled dose, then the patient must be discontinued from the study treatment. Exceptions following discussion between Investigator and Novartis may be possible. Reasons for which exceptions may be possible include:

[redacted]

a. Dosing delays to allow for prolonged steroid tapers to manage Nivolumab-related adverse events are allowed.
b. Dosing delays lasting > 6 weeks from the previous dose that occur for non-Nivolumab-related reasons may be allowed.

All interruptions or modifications must be recorded on the Dosage Administration Record CRF.

In case of study treatment interruption, the evaluation visit schedule should still be followed and assessments performed as per Table 7-1 and Table 7-1b.

Table 6-2 Criteria for omission, delay, or discontinuation of Nivolumab, EGF816 and INC280 for patients receiving Nivolumab and EGF816 or Nivolumab and INC280

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for EGF816 or INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO EGF816 OR INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB
Note: If a toxicity is suspected to be possibly related to both study drugs (EGF816 and nivolumab or INC280 and nivolumab), guidelines pertaining to both study drugs should be followed.		
No toxicity	Maintain dose and schedule	Maintain dose and schedule
Neutropenia (ANC)		
Grade 3 (ANC < 1000 - 500/mm^3)	Omit dose until resolved to ≤ Grade 2, then maintain dose	Dose delay for Nivolumab-related G3 See Section 6.2.4 on resuming Nivolumab
Grade 4 (ANC < 500/mm^3)	Omit dose until resolved to ≤ Grade 2, then reduce dose	Discontinue for Nivolumab related G4 > 7 day duration
Thrombocytopenia		
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, maintain dose If resolved in > 7 days, reduce dose	Dose delay for Nivolumab-related G3 See Section 6.2.4 on resuming Nivolumab Discontinue for Nivolumab-related G3 > 7 days or associated with bleeding
Grade 4 (PLT < 25,000/mm^3)	Omit dose until resolved to ≤ Grade 1, then reduce dose	Discontinue for Nivolumab-related G4
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then reduce dose	Dose delay for Nivolumab-related G3 See Section 6.2.4 on resuming Nivolumab Discontinue for Nivolumab-related G4
Lymphopenia		
≤ Grade 3 (≥ 200/mm^3; ≥ 0.2 x 10^9 /L)	Maintain dose and schedule	Maintain dose and schedule for Nivolumab-related ≤ G3
Grade 4 (< 200/mm^3; < 0.2 x 10^9 /L)	Omit dose until resolved, then reduce dose	Dose delay for Nivolumab-related G4 Nivolumab-related G4 lymphopenia or leukopenia does not require discontinuation See Section 6.2.4 on resuming Nivolumab

[redacted]

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for EGF816 or INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO EGF816 OR INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB
Investigations (Renal)		
Serum creatinine		
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ Grade 1 or baseline, then maintain dose	Dose delay for Nivolumab-related ≥ G2 See Section 6.2.4 on resuming Nivolumab Discontinue for Nivolumab-related G4 See "Renal Adverse Event Management Algorithm" for additional guidance on monitoring and management of any grade events. See Appendix 5.
Grade 3 (> 3.0 - 6.0 x ULN)	Omit dose until resolved to ≤ Grade 1 or baseline, then reduce dose Patients will be instructed to increase their fluid intake until resolution to ≤ Grade 1 or baseline.	
Grade 4 (> 6.0 x ULN)	Discontinue patient from study treatment	
Investigations (Hepatic)		
Isolated Total Bilirubin elevation[b]		
Grade 1 (> ULN – 1.5 X ULN)	Maintain dose level with LFTs monitored	Maintain dose level with LFTs monitored
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, maintain dose If resolved in > 7 days, reduce dose	If baseline total bilirubin is within normal limits, delay dosing for ≥ Grade 2 toxicity If baseline total bilirubin is within the Grade 1 toxicity range, delay dosing for ≥ Grade 3 toxicity See Section 6.2.4 on resuming Nivolumab Discontinue for: • Total bilirubin > 5X ULN For all Grades See "Hepatic Adverse Event Management Algorithm" for additional guidance on monitoring and management of any grade events. See Appendix 5.
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤7 days, reduce dose If resolved in >7 days, discontinue patient from study drug The patient should be monitored weekly (including LFTs (Liver Function Tests)), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilized over 4 weeks	
Grade 4 (> 10.0 x ULN)	Discontinue patient from study treatment The patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilized over 4 weeks	
Isolated AST or ALT elevation		
Grade 2 (> 3.0 – 5.0 x ULN)	Maintain dose level	If baseline AST or ALT is within normal limits, delay dosing for ≥ Grade 2 toxicity

[redacted]

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for EGF816 or INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO EGF816 OR INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose until resolved to ≤ Grade 1 (or ≤ Grade 2 if Grade 2 elevation at baseline, then: If resolved in ≤ 7 days, maintain dose If resolved in > 7 days, reduce dose. See Appendix 6 for additional guidelines on further testing	If baseline AST or ALT is within the Grade 1 toxicity range, delay dosing for ≥ Grade 3 toxicity See Section 6.2.4 on resuming Nivolumab Discontinue for: • AST or ALT > 5 x ULN for > 2 weeks • AST or ALT >10 x ULN See "Hepatic Adverse Event Management Algorithm" for additional guidance on monitoring and management of any grade events. See Appendix 5.
Grade 4 (> 20.0 x ULN)	Discontinue patient from study drug See Appendix 6 for additional guidelines on further testing	
Combined[c] elevations of AST or ALT and total bilirubin[e]		
AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN	For patients with normal baseline ALT or AST or total bilirubin value discontinue from study drug for: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis[d] OR For patients with elevated baseline AST or ALT or total bilirubin value discontinue from study drug for: [AST or ALT > 2.0 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], **combined with** [total bilirubin > 2.0 x baseline AND > 2.0 x ULN] Repeat LFTs[f] as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[f], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilized over 4 weeks. See Appendix 6 for additional guidelines on further testing	Discontinue patient from Nivolumab for: Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN without evidence of cholestasis[d] Repeat LFTs[f] as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[f], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilized over 4 weeks. See "Hepatic Adverse Event Management Algorithm" for additional guidance on monitoring and management of any grade events. See Appendix 5.
Asymptomatic amylase and/or lipase elevation[g]		
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose and schedule.	Maintain dose and schedule
Grade 3 (> 2.0 - 5.0 x ULN)	Omit dose until resolved to Grade ≤ 2, If resolved in ≤ 14 days, maintain dose. If resolved in > 14 days, reduce dose.	Any Grade ≥3 Nivolumab-related isolated amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not

[redacted]

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for EGF816 or INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO EGF816 OR INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB
Grade 4 (> 5.0 x ULN)	Discontinue patient from study treatment	require dose delay or discontinuation. The NVS Medical Monitor should be consulted for such amylase or lipase abnormalities.
Myotoxicity, excluding myocarditis		
Grade 2	Omit dose until resolved to Grade ≤ 1. If resolved to ≤ Grade 1 in ≤ 7 days, maintain dose. If resolved in > 7 days, reduce dose.	Dose delay for any Grade ≥ 2 Nivolumab-related myotoxicity and refer patient to a specialist for assessment and treatment See Section 6.2.4 on resuming Nivolumab
Grade 3	Discontinue patient from study treatment	Discontinue for Grade 3 Nivolumab-related myocarditis Discontinue for Grade 3 Nivolumab-related other myotoxicity lasting longer than 7 days
Grade 4	Discontinue patient from study treatment	Discontinue for Nivolumab-related Grade 4 myotoxicity
Cardiac general, excluding myocarditis		
Grade 2 or 3	Maintain dose and schedule.	Dose delay for any Grade ≥ 2 Nivolumab-related adverse event See Section 6.2.4 on resuming Nivolumab Discontinue for any Grade 3 Nivolumab-related adverse event lasting > 7 days
Grade 4	Discontinue patient from study treatment	Discontinue for any G4 Nivolumab-related adverse event
Myocarditis		
Myocarditis Grade ≥ 2	Mandatory: Permanently discontinue patient from study treatment	Discontinue for Nivolumab
Endocrine		
Grade 2	Maintain dose and schedule	Dose delay for any Grade ≥ 2 Nivolumab-related adverse event See Section 6.2.4 on resuming Nivolumab
Grade 3	Omit dose until resolved to Grade ≤ 2, If resolved in ≤ 14 days, maintain dose If resolved in > 14 days, reduce dose	Grade 3 Nivolumab-related endocrinopathies adequately controlled with only physiologic hormone

[redacted]

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for EGF816 or INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO EGF816 OR INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB
Grade 4	Discontinue patient from study treatment	replacement do not require discontinuation Grade 4 Nivolumab-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the NVS Medical Monitor. See Section 6.2.4 on resuming Nivolumab See "Endocrinopathy Management Algorithm" for additional guidance on monitoring and management of any grade events. See Appendix 5.
Diarrhea/Colitis[h]		
Grade 1	Maintain dose level but initiate anti-diarrhea treatment per institutional standard	Dose delay for any Grade ≥ 2 Nivolumab-related adverse event See Section 6.2.4 on resuming Nivolumab Discontinue for any Grade 3 Nivolumab-related adverse event lasting > 7 days, or any G4 Nivolumab-related adverse event See "GI Adverse Event Management Algorithm" for additional guidance on monitoring and management of any grade events. See Section 6.2.4.
Grade 2	Omit dose until resolved to ≤ grade 1 and initiate anti-diarrhea treatment, then maintain dose If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then reduce dose	
Grade 3	Omit dose until resolved to ≤ grade 1, then reduce dose	
Grade 4	Discontinue patient from study treatment	
Vomiting		
Grade 1 (despite standard anti-emetics)	Maintain dose level	Dose delay for Nivolumab-related Grade 3 See Section 6.2.4 on resuming Nivolumab Discontinue for Nivolumab-related Grade 4
Grade 2 (despite standard anti-emetics)	Omit dose until resolved to ≤ grade 1, then maintain dose level. If vomiting returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then ↓ 1 dose level.	
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	

[redacted]

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for EGF816 or INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO EGF816 OR INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB
Grade 4 (despite standard anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	
Nausea		
Grade 1 or 2 (despite standard anti-emetics)	Maintain dose level	Dose delay for Nivolumab-related Grade 3 See Section 6.2.4 on resuming Nivolumab Discontinue for Nivolumab-related Grade 4
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	
Skin See Section 6.2.2.1 for Skin Toxicity Management Guidelines		
Peripheral edema (General disorders and administration site conditions)		
Grade 1 or 2	Conservative measures such as leg elevation, compression stockings, and dietary salt modification. Consider supportive medications as clinically indicated.	Dose delay for Nivolumab-related Grade 3 See Section 6.2.4 on resuming Nivolumab Discontinue for Nivolumab-related Grade 4
Grade 3	Discontinue dose until resolved to ≤ Grade 1, then ↓ 1 dose level	
Grade 4	Discontinue INC280	
Fatigue/Asthenia		
Grade 3	Omit dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, maintain dose If resolved in > 7 days, reduce dose	Grade 2 Nivolumab-related fatigue does not require Nivolumab delay. Dose delay for any Grade ≥ 3 Nivolumab-related adverse event See Section 6.2.4 on resuming Nivolumab Discontinue for any Grade 3 Nivolumab-related adverse event lasting > 7 days, or any G4 Nivolumab-related adverse event
Grade 4	Omit dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, maintain dose If resolved in > 7 days, reduce dose	
Any Neurological toxicity		
Grade 2	Omit dose until resolved to ≤ grade 1	Dose delay for any Grade ≥ 2 Nivolumab-related adverse event See Section 6.2.4 on resuming treatment Discontinue for any Grade 3 Nivolumab-related adverse event lasting > 7 days, or any G4 Nivolumab-related adverse event See “Neurological Adverse Event Management Algorithm” for additional guidance on monitoring and management of any grade events. See Appendix 5.
Grade 3 or 4	Omit dose. Neurological assessments must be repeated at least twice a week until resolution to < CTCAE grade 1. Unscheduled MRI and gadolinium enhanced T1 imaging may also be conducted to evaluate patients for intramyelinic edema like lesions, brain metastases and other unanticipated CNS occurrences. An EEG may be performed to monitor for physiological changes in brain activity.	

[redacted]

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for EGF816 or INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO EGF816 OR INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB
Ocular		
Grade 2	Omit dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, maintain dose If resolved in > 7 days, reduce dose	Dose delay for any Grade ≥ 2 Nivolumab-related adverse event See Section 6.2.4 on resuming Nivolumab Discontinue for any Grade 2 Nivolumab-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment Grade 3 Nivolumab-related uveitis of any duration requires discontinuation Discontinue for any Grade 3 Nivolumab-related adverse event lasting > 7 days, or any G4 Nivolumab-related adverse event
Grade 3	Discontinue patient from study treatment	
Grade 4	Discontinue patient from study treatment	
Pulmonary toxicity other than ILD/Pneumonitis		
Grade 2	Omit dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, maintain dose If resolved in > 7 days, reduce dose	Dose delay for any Grade ≥ 2 Nivolumab-related adverse event See Section 6.2.4 on resuming Nivolumab Grade ≥3 Nivolumab-related pneumonitis of any duration requires discontinuation Discontinue for any Grade 3 Nivolumab-related pulmonary adverse event other than pneumonitis lasting > 7 days, or any G4 Nivolumab related pulmonary adverse event other than pneumonitis See “Pulmonary Adverse Event Management Algorithm” for additional guidance on monitoring and management of any grade events. See Appendix 5.
Grade 3	Omit dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, maintain dose If resolved in > 7 days, reduce dose	
Grade 4	Discontinue patient from study drug	
ILD like events/Pneumonitis		
Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. In addition, withhold INC280 for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage. Any grade pneumonitis/interstitial lung disease should be considered possibly related to BOTH study drugs (nivolumab and EGF816 or nivolumab and INC280). For the follow-up and management of ILD like events/pneumonitis, also refer to Appendix 5, Pulmonary Adverse Event Management Algorithm.		

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for EGF816 or INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO EGF816 OR INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB
Grade 1 Asymptomatic, radiographic findings only	Continue EGF816 at same dose level. Interrupt INC280 during diagnostic workup for ILD/Pneumonitis. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue INC280. Only in the absence of a diagnosis of ILD/Pneumonitis, INC280 may be restarted at the same dose. If it recurs after resumption of study drug permanently discontinue INC280.	Consider delay of Nivolumab dosing.
Grade 2 Symptomatic, not interfering with activity daily living (ADL)	Interrupt study drug dose during diagnostic workup for ILD until improvement to ≤ Grade 1. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue study drug. In the absence of a diagnosis of ILD/Pneumonitis, study drug may be restarted following guidelines: if symptoms resolve to ≤ Grade 1 in ≤ 7 days reduce study drug by 1 dose level. If symptoms fail to resolve within 7 days or recur after resumption of study drug at decreased dose, permanently discontinue study drug.	Mandatory: Delay Nivolumab dosing during diagnostic work up for ILD until improvement to ≤ Grade 1. Exclude infections and other etiologies. See Section 6.2.4 on resuming Nivolumab. See “Pulmonary Adverse Event Management Algorithm” for additional guidance on monitoring and management in Appendix 5.

[redacted]

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for EGF816 or INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO EGF816 OR INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB
Grade 3 Symptomatic, interfering with ADL; O2 indicated and Grade 4 Life-threatening; ventilatory support indicated	Permanently discontinue study drug.	Permanently discontinue Nivolumab.
Hypersensitivity		
	As per Non-laboratory AE guidance	See Table 6-7 for treatment of Nivolumab-related infusion reactions Grade >/= 3 Nivolumab-related bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
Other Non-laboratory adverse events		
Grade 1 or 2	Maintain dose and schedule.	Dose delay for any Grade ≥ 2 Nivolumab-related adverse event See Section 6.2.4 on resuming Nivolumab Discontinue for any Grade 3 Nivolumab-related adverse event lasting > 7 days, or any G4 Nvolumab-related adverse event
Grade 3	If ongoing at time of next scheduled drug – omit scheduled dose If resolved to ≤ grade 1 and prior to scheduled dose; may proceed with scheduled dose	
Grade 4	Discontinue patient from study treatment	
Other laboratory adverse events		
	As per Non-laboratory AE guidance above	Grade 2 or 3 Nivolumab-related laboratory abnormalities other than specified above do not require a Nivolumab delay. Dose delay for any Grade ≥ 3 Nivolumab-related adverse event See Section 6.2.4 on resuming Nivolumab
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE Version v4.03) [b] If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator. [c] "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the		

[redacted]

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for EGF816 or INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO EGF816 OR INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB

situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction.

[d] "Cholestasis" defined as: ALP elevation [>2 x ULN and R value <2] in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R≤2), hepatocellular (R≥5), or mixed (R>2 and <5) liver injury

[e] For toxicity defined as related to EGF816 or INC280; If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, restart the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction.

[f] LFTs include albumin, ALT, AST, GGT, total bilirubin (fractionated (direct and indirect) if total bilirubin >2.0 x ULN), alkaline phosphatase (fractionated (quantification of isoforms) if alkaline phosphatase > 2.0 x ULN) and GGT. For isolated elevations of any grade of alkaline phosphatase and/or gamma-glutamyl transpeptidase (GGT), maintain dose level.

[g] A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 3 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study drug.

[h] antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea

6.2.2 Follow-up for toxicities

In case of isolated elevations in total bilirubin, AST or ALT, or ILD/Pneumonitis additional follow-up evaluations are recommended as outlined in Table 6-3:

[redacted]

Table 6-3 Follow-up evaluations for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION
HEPATIC	
Isolated total bilirubin elevation	
CTCAE Grade 1	Monitor LFTs per protocol or more frequently if clinically indicated
CTCAE Grade 2	Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN
CTCAE Grade 3	Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. If resolved in > 7 days, after discontinuing the patient from INC280 permanently, the patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks
CTCAE Grade 4	After discontinuing the patient from INC280 permanently, the patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 week
Isolated AST/ALT elevation	
CTCAE Grade 2 For patients with baseline value ≤ 3.0 x ULN	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
For patients with baseline value > 3.0 - 5.0 x ULN	Monitor LFTs per protocol or more frequently if clinically indicated
CTCAE Grade 3 -For elevation > 5.0 - 10.0 x ULN: For patients with baseline value ≤ 3.0 x ULN	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
For patients with baseline value > 3.0 - 5.0 x ULN:	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs, weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN
CTCAE Grade 3 For AST/ALT elevation > 10.0 - 20.0 x ULN:	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ baseline
CTCAE Grade 4	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
ILD/Pneumonitis	
CTCAE Grade 1	CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression- re-image at least every 3 weeks Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection Monitoring of oxygenation via pulse oximetry recommended Consultation of pulmonologist recommended

TOXICITY	FOLLOW-UP EVALUATION
CTCAE Grade 2	CT scan (high-resolution with lung windows) • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Pulmonary function tests [a] - if normal at baseline, repeat every 8 weeks • Bronchoscopy with biopsy and/or BAL recommended [c] Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated) [b]
CTCAE Grade 3 and Grade 4	CT scan (high-resolution with lung windows) Clinical evaluation and laboratory work-up for infection Consult pulmonologist Pulmonary function tests [a]-if < normal, repeat every 8 weeks until ≥ normal Bronchoscopy with biopsy and/or BAL if possible [c] Treat with IV steroids (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) [b]. If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication
*Note: this table refers only to the evaluation schedule to monitor selected toxicities. Refer to Table 6-2 for dose modifications required for applicable toxicities [a] PFT (Pulmonary function tests) to include: diffusing capacity corrected for hemoglobin (DLCO); spirometry; resting oxygen saturation Guideline for significant deterioration in lung function: Decrease in spirometry and/or DLCO of 30% and/or O_2 saturation ≤ 88% at rest on room air. [b] Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. Consider tapering dosage at end. [c] If bronchoscopy is performed, bronchoalveolar lavage (BAL) should be done where possible to exclude alveolar hemorrhage, opportunistic infections, cell count + determination lymphocyte CD4/8 count where possible.	

6.2.2.1 Guidelines for prevention and management of rash/skin toxicities

For all patients, guidelines for the prevention and symptomatic management of skin toxicities are provided in Table 6-4. Additional guidelines for the management of rash/skin toxicities specific to Group 1 and Group 2 patients are provided below.

[redacted]

Table 6-4 Guidelines for prevention and symptomatic care of rash/skin toxicities for all patients

Type of care	Action
Prevention/Prophylaxis Starting from Da y 1 for all patients	• Avoid unnecessary exposure to sunlight • Apply broad-spectrum sunscreen with SPF≥15 at least twice daily • Use thick, alcohol-free emollient cream (e.g. glycerine and cetomacrogol cream) on dry areas of the body at least twice daily
Symptomatic care*	• Pruritic lesions: cool compresses and oral antihistamine therapies • Desquamation: thick, alcohol-free emollient cream and mild soap • Paronychia: antiseptic bath and topical antibiotics; if no improvement, consult dermatologist • Infected lesions: appropriate topical or systemic antibiotics
*Patients who develop rash/skin toxicities should be evaluated by a qualified physician and receive symptomatic and supportive care management.	

Group 1 patients

Rash, particularly maculopapular rash or rash pruritic, is an adverse event frequently observed following treatment with EGF816. Rash is also a common adverse event associated with nivolumab. Patients must be closely monitored for any signs/symptoms related to rash/skin toxicities. Recommended guidelines for management and dose modification of rash/skin toxicities are provided in Table 6-4 and Table 6-5. These guidelines constitute guidance to the Investigator and may be supplemented or modified on a case-by-case basis after discussion with Novartis. In addition:

1. Educate all patients on the importance of notifying the investigator immediately (e.g., by telephone) if a rash appears. Investigators are to contact Novartis if a patient develops a grade 2 or higher rash.
2. Educate all patients on the guidelines for prevention of rash/skin toxicity (see Table 6-4).
3. All rashes occurring on study for patients receiving the combination are to be considered possibly related to **both** EGF816 and nivolumab, even after the discontinuation of nivolumab (due to its long half-life).
4. For all rashes, institute interventions related to rash as outlined in Table 6-4 and Table 6-5.

[redacted]

Table 6-5 Guidelines for dose modification and management related to rash for Group 1 patients[1]

Note: For any grade Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, permanently discontinue EGF816.	
CTCAE Grade	**Actions**
Grade 1	• Continue EGF816 at same dose level • See "Skin Adverse Event Management Algorithm" (Section 14.5) for actions to be taken if rash persists more than 1-2 weeks • Initiate appropriate symptomatic care, if not already instituted (refer to Table 6-4) • Use mild-strength topical steroid (e.g. 1% hydrocortisone cream) on affected areas • Re-assess after 1 week • If systemic steroids are instituted based on nivolumab guidelines (Section 14.5), follow the nivolumab guidelines for the systemic steroid course.
Grade 2	• Interrupt EGF816 until recovered to ≤ Grade 1. Once rash has recovered to ≤ Grade 1, restart EGF816 at one level reduced from the previous dose level[2] • See "Skin Adverse Event Management Algorithm" (Section 14.5) for follow-up actions if rash persists > 1-2 weeks or recurs. • Initiate appropriate symptomatic care, if not already instituted (refer to Table 6-4) • Use moderate-strength topical steroid (e.g. 2.5% hydrocortisone cream or 0.5% fluticasone cream) on affected areas PLUS low-dose oral steroid (e.g. prednisone 5mg-10mg PO QD for 1 week) with taper. If systemic steroids are instituted based on nivolumab guidelines (Section 14.5), follow the nivolumab guidelines for the systemic steroid course. • Re-assess after 1 week
Grade 3	• Interrupt EGF816 until rash recovers to ≤ Grade 1. Once recovers to ≤ Grade 1, restart EGF816 at one level reduced from the previous dose level[2]. • If no recovery to ≤ Grade 2 within 3 weeks, permanently discontinue EGF816 • Initiate appropriate symptomatic care, if not already instituted (Refer to Table 6-4) • Start systemic steroids and follow additional instructions per nivolumab guidelines (See Section 14.5, "Skin Adverse Event Management Algorithm") • Consult dermatologist **If re-initiating EGF816 after Grade 3 rash**: • Oral antihistamine therapies (e.g. levocetirizine 5mg QD, desloratadine 5mg QD, or fexofenadine 180 mg QD) should be given concurrently with EGF816 for 4 weeks when restarting treatment. • Patients who develop more than 1 episode of Grade ≥ 3 rash will be permanently discontinued from EGF816
Grade 4	• Permanently discontinue EGF816 • Initiate appropriate symptomatic care, if not already instituted (Refer to Table 6-4) • Follow instructions for systemic steroid treatment in nivolumab guidelines (See Section 14.5, "Skin Adverse Event Management Algorithm") • Consult dermatologist

[redacted]

Note: For any grade Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, permanently discontinue EGF816.	
CTCAE Grade	**Actions**
[1] For all grades of rash, consider skin biopsy for pathologic evaluation. [2] A maximum of 2 dose reductions is allowed. Patients who require further dose decrease after 2 dose reductions should be discontinued from study drug. Escalation **by one level** to previous dose level may be considered if no rash is evident after 4 weeks of uninterrupted study drug at the reduced dose level. Re-escalation can only be done once.	

Group 2 patients

The guidelines in Table 6-6 apply to patients in Group 2.

[redacted]

Table 6-6 Criteria for omission, delay, or discontinuation of Nivolumab and INC280 for skin toxicity for patients receiving Nivolumab and INC280

Worst toxicity CTCAE[a] (unless otherwise specified)	Recommended dose modifications for INC280 During a cycle of therapy TOXICITY DEFINED AS RELATED TO INC280	Recommended dose modifications for Nivolumab During a cycle of therapy TOXICITY DEFINED AS RELATED TO NIVOLUMAB
Note: For any grade Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, permanently discontinue INC280 and nivolumab.		
Grade 1	Maintain dose level of INC280. Consider initiating institutional standard and/or local practice guidelines to treat skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids per institutional standard).	Dose delay for any Grade ≥ 3 Nivolumab-related adverse event See Section 6.2.4 on resuming Nivolumab Discontinue for or any Grade 3 Nivolumab-related adverse event lasting > 7 days, or any G4 Nivolumab-related adverse event See "Skin Adverse Event Management Algorithm" (Appendix 5) for additional guidance on monitoring and management of any grade events.
Grade 2	Maintain dose level of INC280, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids per institutional standard). If no recovery or worsened within 1 week, interrupt study drug until recovery to ≤ Grade 1. Once rash has recovered to ≤ Grade 1, then restart at reduced dose.	
Grade 3, despite skin toxicity therapy	Omit INC280 until resolved to Grade ≤ 1, and then: initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids). Resume at reduced dose. If no recovery to ≤ Grade 2 within 3 weeks, permanently discontinue study treatment. Patients who develop more than 1 episode of Grade ≥3 rash will be permanently discontinued from study treatment.	
Grade 4, despite skin toxicity therapy	Discontinue patient from study treatment.	
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE Version v4.03)		

[redacted]

6.2.3 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g., biliary tract) may be warranted.
- Obtain PK sample, as close as possible to last dose of study drug.
- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

6.2.4 Criteria to resume treatment with Nivolumab after dose delay

Subjects may resume treatment with Nivolumab when the Nivolumab-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT **OR** total bilirubin

[redacted]

- Nivolumab-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by Novartis.
- Nivolumab-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with Novartis

Dose delay of Nivolumab which results in treatment interruption of > 6 weeks require treatment discontinuation, with exceptions as noted above. There will be no dose reductions for Nivolumab.

6.2.5 Treatment of Nivolumab-related infusion reactions and other immune-related AEs

Since Nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to Novartis and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

Additionally, immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: Gastrointestinal; Renal; Pulmonary; Hepatic; Endocrinopathy; Skin; Neurological; and Myocarditis. Management Algorithms can be found in the Nivolumab IB and Appendix 5.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

[redacted]

Table 6-7 Guidelines for treatment for Nivolumab induced infusion reactions

Grade	Recommended Intervention
For Grade 1 symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated):	Remain at bedside and monitor patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional Nivolumab administrations
For Grade 2 symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti inflamatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for < 24 hours):	Stop the Nivolumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, then no further Nivolumab will be administered at that visit. For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before Nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life threatening; pressor or ventilatory support indicated):	Immediately discontinue infusion of Nivolumab. Begin an IV infusion of normal saline and treat the patient as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery of the symptoms
In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment)	Symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

[redacted]

6.3 Concomitant medications

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed except as specifically prohibited in Section 6.3.2. The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug combination. All medications (other than study drug combination) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Surgical and Medical Procedures CRF

Steroids

Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Systemic corticosteroids ≤ 10 mg daily prednisone equivalent are allowed (higher doses to treat a drug-related immune-mediated AE must be tapered to 10 mg or lower before resuming nivolumab). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

6.3.1 Permitted concomitant therapy requiring caution and/or action

INC280 is a moderate CYP1A2 inhibitor. Co-administration of INC280 increased the sensitive CYP1A2 probe substrate (caffeine) AUC by 135%. The dose of CYP1A2 substrates with narrow therapeutic index may need to be reduced when used concurrently with INC280, as INC280 may increase their exposure. Consult the product information of the concomitant drug for dose adjustment.

Co-administration of INC280 increased Pgp substrate (digoxin) exposure (AUC and Cmax by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUC and Cmax by 108% and 204%, respectively). Monitor patients closely for symptoms of increased exposure to Pgp or BCRP substrates. Consult the concomitant Pgp or BCRP substrate product information when considering dose adjustment.

Co-administration of INC280 with a strong CYP3A4 inhibitor (itraconazole) increased INC280 AUC by 40%. There was no change in INC280 Cmax. Exercise caution when using a strong CYP3A4 inhibitor concurrently with INC280.

While the data on the concurrent use of PPI and food have to be considered preliminary as they have been generated in a small cohort of patients of the study [CINC280A2108], the decrease in exposure imposes caution on the use of PPI when INC280 is taken with no regards of food.

Short acting gastric acid modulators containing aluminum hydroxide and magnesium hydroxide, or calcium carbonate can be taken. However, it is recommended that these drugs be taken at least 3 hours before or 3 hours after administration of INC280. H2 receptor antagonists should be avoided. If patients are using H2 receptor antagonists during the course of this study, patients should not take H2 receptor antagonists for at least 2 hours after administration of INC280. In

[redacted]

addition, the next scheduled dose of INC280 should be administered at least 8 hours after taking H2 receptor antagonists.

INC280 is a weak to moderate inhibitor of CYP2C8, CYP2C9 and CYP2C19 *in vitro*. Substrates of CYP2C8, CYP2C9 and CYP2C19 with a narrow therapeutic window should be administered with caution for patients treated with INC280.

EGF816 is a moderate to weak inhibitor for CYP2D6 and CYP2C8. The sensitive substrates for these CYP isoforms, should be administered with caution for EGF816 and Nivolumab combination.

EGF816 is a P-gp substrate and a moderate inhibitor of BCRP and human multidrug and toxin extrusion (MATE; 1 and 2K) transporters. Caution should be exercised when potent P-gp inhibitors, BCRP and MATE substrates are concurrently used in the EGF816/Nivolumab combination.

INC280 displayed inhibition of P-gp, BCRP, MATE, OATP1B1 and OATP1B3. Sensitive substrates for P-gp, BCRP, MATE and OATP transporters should also be administered with caution for INC280/Nivolumab combinations.

Localized palliative non-invasive therapy, such as radiotherapy, is allowed for the treatment of symptomatic bone or CNS lesions. EGF816 should be interrupted at least 5 days prior to such therapy if medically safe to delay local therapy, and may be resumed ≥3 days after completion of therapy if all AEs related to the intervention have resolved to ≤ Grade 1. INC280 should be interrupted at least 2 days prior to such therapy if medically safe to delay local therapy, and may be resumed ≥3 days after completion of therapy if all AEs related to the intervention have resolved to ≤ Grade 1. No washout period is required for nivolumab prior to local therapy; nivolumab may be resumed ≥ 2 weeks after completion of local therapy if all AEs related to the intervention have resolved to ≤ Grade 1.

Please refer to Table 14-1 for a full list of concomitant medications to be used with caution.

6.3.2 Prohibited concomitant therapy

EGF816 is mainly metabolized by CYP3A4, therefore strong inhibitors and strong inducers of CYP3A4 (Table 14-2) should not be used concomitantly with EGF816. Co-administration of INC280 with a strong CYP3A4 inducer (rifampicin) decreased INC280 AUC by 66% and Cmax by 56%. Concurrent use of strong CYP3A4 inducers is prohibited for patients treated with INC280 as decreased INC280 exposure may lead to reduced efficacy.

For INC280, drugs with known risk of causing TdP are prohibited (Table 14-2). Study treatment must be interrupted as long as the patient requires therapy with QT prolonging agent.

Immunosuppressive agents and immunosuppressive doses of systemic corticosteroids (except as stated above) are prohibited, except when utilized to treat a drug-related adverse event.

Live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines) should not be administered while a patient is dosed with EGF816 and for 30 days after the last dose of EGF816.

Concomitant antineoplastic therapy (including radiotherapy and surgery) or other investigational treatment is prohibited except as described in Section 6.3.1.

[redacted]

6.4 Patient numbering, treatment assignment, or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

Once assigned, the Subject No. must not be reused for any other patient and the Subject No. for that individual must not be changed, even if the patient is re-screened.

6.4.2 Treatment assignment or randomization

The assignment of the patient to the treatment groups will be coordinated by Novartis. No randomization will be performed for this study.

6.5 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient and/or administered to the patient by authorized site personnel only. All dosage prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.5.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but will not supply information about the patient. EGF816 and INC280 will be supplied by Novartis. EGF816 25 mg, 50 mg, and 100 mg capsules will be packaged in high density polyethylene (HDPE) bottles. INC280 50 mg, 150 mg, and 200 mg tablets will be packaged in HDPE bottles. Nivolumab will be supplied in vials as a solution for infusion. Instructions for preparation and dispensation for Nivolumab are described in the Nivolumab Investigator Brochure.

6.5.2 Study drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the **study treatment** should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

[redacted]

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

At the day of a scheduled visit to the clinic, the patient will take either EGF816 or INC280 according to the assigned treatment group and will be given a Nivolumab infusion, at the clinic under the supervision if the Investigator or his designee. For all other study days, the patient will take EGF816 or INC280 at home depending on the assigned treatment group.

The time of dose administrations on days when PK blood samples are drawn must be recorded in the Dosage Administration Record eCRF.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 and Table 7-1b list all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation.

No CRF will be used as a source document.

For all visits, with the exception of PK sampling, there is a +/- 3 days window on assessments to take into account scheduling over public or religious holidays, **if not explicitly stated otherwise**. For PK sampling, time windows are defined in Section 7.2.3. Should there be a need to modify the PK schedule due to dose interruptions, please contact Novartis to discuss sampling schedules.

[redacted]

Disease progression and overall survival follow-up visits have a +/- 7 days window.

For imaging assessments, a +/- 7 days window is allowed, except for the first post baseline assessment and for confirmatory scans (+7 days window only permitted). All screening assessments, including baseline imaging assessments, must be completed within 28 days before the first dose. Laboratory assessments performed as part of the screening evaluations and within 72 hours of the first dose of study treatment, are not required to be repeated on the first dosing day.

Molecular pre-screening assessments can be performed any time prior to the initiation of screening.

PK samples will be collected according to Table 7-6, Table 7-7, Table 7-8, Table 7-9, and Table 7-10.

Biomarker sampling will be conducted as outlined in Table 7-11.

All assessments should be performed as outlined in Table 7-1 and as clinically indicated.

Following the approval of protocol amendment 8, the ongoing patients will follow a reduced schedule of safety assessments as specified in Table 7-1b. The assessment schedule specified in Table 7-1 will become obsolete. Other assessments may be performed at the discretion of investigator as per the standard of care at site.

[redacted]

Table 7-1 Visit evaluation schedule

			Screening Phase		Treatment Phase											Follow-Up			
	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Subsequent cycles		EoT	30 day safety F/U	100-day Safety F/U (end of study)	Disease progression F/U	Survival (every 12 weeks)
Day of Cycle				**-28 to 1**	**1**	**8**	**15**	**22**	**1**	**14**	**15**	**22**	**1**	**15**					
Obtain Molecular Pre-screening Informed Consent (if applicable)	D	7.1.1.	X																
Obtain Informed Consent	D	7.1.2.		X															
Demography	D	7.1.2.3.	X	X															
Inclusion/exclusion criteria	D	5.2/5.3.		X															
Medical history/Current medical conditions	D	7.1.2.3.		X															
Diagnosis and extent of cancer	D	7.1.2.3.		X															
Prior antineoplastic therapies	D	7.1.2.3.		X															
Smoking history	D	7.1.2.3.		X															
Prior/concomitant medications	D	7.1.2.3.		CONTINUOUSLY															
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5.													X	X	X	X	X
Physical examination	S	7.2.2.1.		X	X	X	X		X		X	X	X		X	X	X		
Vital signs	D	7.2.2.2.		X	X	X	X		X	X[1]	X	X	X	X	X	X	X		
Pulse Oximetry	D	7.2.2.2.		X	X		X		X		X		X	X		X	X		
Height	D	7.2.2.3.		X															

[redacted]

			Screening Phase		Treatment Phase											Follow-Up			
	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Subsequent cycles		EoT	30 day safety F/U	100-day Safety F/U (end of study)	Disease progression F/U	Survival (every 12 weeks)
Day of Cycle				**-28 to 1**	**1**	**8**	**15**	**22**	**1**	**14**	**15**	**22**	**1**	**15**					
Weight	D	7.2.2.3.		X	X		X		X		X		X	X	X	X	X		
Performance status	D	7.2.2.4.		X	X				X				X		X	X	X		
HIV testing[8]	D	7.2.2.5.2.		X[8]															
Hepatitis B and C testing	D	7.2.2.5.2.		X															
Hematology	D	7.2.2.5.1.		X	X	X	X	X[1]	X	X[2]	X	X	X	X	X	X	X		
Chemistry	D	7.2.2.5.2.		X	X	X	X	X[1]	X	X[2]	X	X	X	X	X	X	X		
Coagulation	D	7.2.2.5.3.		X															
Serum Pregnancy Test	D	7.2.2.5.4.		X	X				X				X		X	X			
Urine Pregnancy Test[9]	S																X		
Tumor evaluation as per RECIST v1.1 CT/MRI	D	7.2.1 /7.1.5.		X									End of every 2 cycles, Q8 wks up to C12, then end of every 12 wks from C13 to C24, then every 24 weeks to C36, then every 52 weeks from C37.		X			X	
ECG	D	7.2.2.6.		X	X		X		X				X		X				
AEs	D	8.1.	X	X		Continuously													
Collection of archival or newly obtained tumor sample	D	7.1.1. 7.2.4.	X																

[redacted]

			Screening Phase		Treatment Phase											Follow-Up			
	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Subsequent cycles		EoT	30 day safety F/U	100-day Safety F/U (end of study)	Disease progression F/U	Survival (every 12 weeks)
Day of Cycle				**-28 to 1**	**1**	**8**	**15**	**22**	**1**	**14**	**15**	**22**	**1**	**15**					
Collection of newly obtained tumor sample	D	7.1.1. 7.2.4.		X[6]									X (C3D1) X (C5D1-optional) X (C7D1-optional)		X optional				
[redacted]																			
Companion[3] Sample protocol Assessments (consent, inclusion, exclusion, sample collection, biopsy related serious adverse events)	D	7.2.4.	X	X	X (upon disease progression)													X	
Nivolumab dosing (every 2 weeks)	D	6.1.1.			X		X		X		X		X	X					
EGF816 Dosing	D	6.1.1.			Continuously														
INC280 Dosing	D	6.1.1.			Continuously														
EGF816 and INC280 PK blood sampling (Safety monitoring cohort only)	D	7.2.3.2.			X[4]	X[4]	X		X				X (cycles 4,6, 8 & upon disease progression)						

[redacted]

			Screening Phase		Treatment Phase										EoT	Follow-Up			
	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Subsequent cycles			30 day safety F/U	100-day Safety F/U (end of study)	Disease progression F/U	Survival (every 12 weeks)
Day of Cycle				**-28 to 1**	**1**	**8**	**15**	**22**	**1**	**14**	**15**	**22**	**1**	**15**					
Nivolumab PK blood sampling (All patients)	D	7.2.3.2.			X		X		X				X (cycles 4, 8) then every 8th cycle after C8D1& upon disease progression			X	X		
Meal Record	D	7.2.3.1.					X						X (cycles 4,6, 8)						
EGF816 and INC280 PK blood sampling (After safety monitoring cohort)	D	7.2.3.2.					X		X				X (cycles 4,6, 8 & upon disease progression)						
[redacted]																			
Survival contact (telephone call)	D	7.1.5.																	X

[redacted]

			Screening Phase		Treatment Phase											Follow-Up			
	Category	Protocol Section	Molecular Pre-screening	Screening	Cycle 1				Cycle 2				Subsequent cycles		EoT	30 day safety F/U	100-day Safety F/U (end of study)	Disease progression F/U	Survival (every 12 weeks)
Day of Cycle				**-28 to 1**	**1**	**8**	**15**	**22**	**1**	**14**	**15**	**22**	**1**	**15**					

1. For patients in safety monitoring cohort only
2. For patients in safety monitoring cohort, hematology and chemistry assessments will be performed on C2D14 instead of Cycle 2 D15.
3. Mandatory if participating in the Companion Sample Collection, unless medically unsafe or infeasible. See companion sample collection protocol for further information
4. For EGF816 only
5. For US patients cMet detection/confirmation of cMet dysregulation will be performed on archival tumor sample only
6. Sample will not be collected if a newly obtained tumor sample has already been obtained at pre-screening for the purpose of [redacted]. An archival sample may be submitted instead of a newly obtained tumor sample after documented discussion with Novartis, if it was recently obtained and there has been no intervening systemic anti-neoplastic therapy.
7. Collect at screening or anytime thereafter.
8. HIV testing will be done at screening for patients in Germany
9. Monthly urine pregnancy tests should be performed after the 30 day safety follow up visit and should continue until approximately 23 weeks after discontinuation of the study treatment. Urine pregnancy test results should remain with the patient records and do not need to be included in the clinical database.

[redacted]

Table 7-1b Visit evaluation schedule (effective after protocol amendment 08 is approved)

				Follow Up			
	Category	**Day 1 of every other cycle (every 8 weeks)**	**EoT**	**30-day safety F/U**	**100-day Safety F/U (end of study)**	**Disease progression F/U**	**Survival (every 12 weeks)**
Physical examination	S	X	X				
Vital signs	D	X	X				
Hematology	D	X (on Day 1 of EVERY cycle during the first 13 cycles)	X				
Chemistry	D	X (on Day 1 of EVERY cycle during the first 13 cycles)	X				
Serum pregnancy test	D	X (on Day 1 of EVERY cycle)	X	X			
Urine pregnancy test	S				X		
Tumor evaluation as per RECIST v1.1 CT/ MRI	D	Every 8 weeks up to C12, then every 12 weeks from C13 to C24, then every 24 weeks from C25 to C36, then every 52 weeks from C37 onwards until 12 months has elapsed since last patient first treatment	X			X (every 12 weeks with ± 7 days window, until 12 months has elapsed since last patient first treatment)	
ECG	S	X	X				
Adverse event	D	Continuous					
Concomitant medications	D	Continuous					
New antineoplastic therapy since discontinuation of study treatment			X	X			

[redacted]

				Follow Up			
	Category	**Day 1 of every other cycle (every 8 weeks)**	**EoT**	**30-day safety F/U**	**100-day Safety F/U (end of study)**	**Disease progression F/U**	**Survival (every 12 weeks)**
Collection of newly obtained tumor sample	D		X (optional)				
[redacted]							
EGF816/ INC280 dosing	D	Continuous					
Nivolumab dosing	D	Continuous (every 2 weeks on Day 1 & Day 15 of every cycle for up to 2 years)					
Survival contact (telephone contact)	D						X

[redacted]

7.1.1 Molecular pre-screening

An archival or a newly obtained tumor sample will be submitted to a Novartis-designated central laboratory for molecular pre-screening. This sample will be used to detect the T790M mutation in the EGFR gene for Group 1 patients, and to determine cMet status by IHC and FISH for Group 2 patients (for US patients, cMet testing will be performed on an archival tumor sample only). Only those patients whose tumors are EGFR T790M-mutated will be eligible to screen for Group 1. To be eligible for Group 2, cMet IHC and FISH status must be successfully determined centrally, and documentation of EGFR wt status must be available (local mutation testing for EGFR is preferred, but central testing can be performed if local results are not available). Results of central pre-screening analysis will be communicated back to the investigator.

Upon positive determination that the sample submitted contains the required EGFR T790M mutation and that cMet molecular status has been determined, the patient may sign the study's main Informed Consent to begin screening procedures.

Additionally for all patients enrolled into this study, a newly obtained tumor sample or a recently-obtained archival tumor sample will be collected for [redacted] analyses as outlined in Table 7-11.

7.1.2 Screening

The IRB/IEC study approved informed consent form (ICF) must be signed and dated before any screening procedure is performed. Procedures which are part of the clinical routine during the initial diagnostic work-up of the patient may be obtained before obtaining the ICF. A copy of the ICF must be given to the patient or to the person signing the form. The investigator or his designee must record the date when the study informed consent was signed in the medical records of the patient.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. For details please refer to Table 7-1.

Screening assessments must be done within 28 days prior to the first dose of the study medication with the exception of the pregnancy test, which must be performed within 72 hours of the first dose. Clinical and radiological tumor assessment by RECIST v1.1 (Appendix 4) should be conducted within 1 week (7 days) prior to the first dose of study treatment; however tumor assessments up to 4 weeks (28 days) prior to the first dose will be acceptable. The tumor assessment during the screening phase will be used to determine future responses and/or progression.

7.1.2.1 Enrollment process

When the patient is considered eligible, the investigator or clinical site should complete the Patient Registration Form and send it to Novartis.

After the patient signs the study Informed Consent form, the investigator or clinical site should determine patient eligibility. The investigator or site staff should complete patient registration

[redacted]

form and send it to Novartis. The allocation of patients to treatment groups will be handled by Novartis.

7.1.2.2 Information to be collected on screening failures

Patients who signed a molecular pre-screening ICF but are considered ineligible after molecular pre-screening, as well as patients who are found not eligible after signing the main study consent will be considered as screening failures, and data will be handled in the same manner.

The reason for molecular pre-screening failure or screening failure will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported.

7.1.2.3 Patient demographics and other baseline characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, diagnosis and extent of tumor, details of prior anti-neoplastic treatments and any other assessments that are done for the purpose of determining eligibility for inclusion in the study. All medications and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) taken within 4 weeks prior to first dose of study drug must be recorded on the eCRF. Smoking history will be recorded on the eCRF at screening

7.1.3 Treatment period

A treatment cycle is defined as 28 days (4 calendar weeks) for the purposes of scheduling procedures and evaluations. Please refer to Table 7-1 and Table 7-1b for details of the timing of required assessments and Section 7.1 for visit windows.

During the treatment period, the patient is obliged to follow the investigators instructions with regards to contraception, concomitant medications and dosing regimen.

There is no fixed treatment duration.

Patients will be treated until patient experiences unacceptable toxicity, progressive disease and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent as described in Section 7.1.4.2, or the patient is transferred to a Novartis roll-over study or an alternative treatment option that can continue to provide study treatments.

Following the approval of protocol amendment 08, the maximum treatment duration for Nivolumab cannot exceed 2 years. Afterwards, patients who have received Nivolumab beyond 2 years will discontinue Nivolumab treatment and continue on EGF816/INC280 alone. In patients who have previously discontinued EGF816/INC280 and have been receiving Nivolumab alone, patients will discontinue Nivolumab treatment, have an end of treatment visit and continue with the safety and survival follow-up as per Table 7-1b.

[redacted]

7.1.4 End of treatment visit including study completion and premature withdrawal

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, and within 14 days of the last dose of study drugs or within 14 days of the decision to permanently discontinue study treatment, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. For purposes of this study, the term "discontinue study treatment" will refer to the discontinuation of both investigational agents. Patients who meet the criteria for exceptional cases and/or a discontinuation criteria that applies to only one of the investigational agents will not be scheduled to undergo an EOT until all investigational agents are discontinued.

If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit.

An End of Treatment Phase Disposition CRF page should be completed, giving the date and reason for stopping the study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit but do not formally withdraw consent, will be assessed via safety evaluations as outlined in Table 7-1 and Table 7-1b during the 100 days following the last dose of study treatment. Patients should return for 30-day safety follow-up (see Section 7.1.5), disease progression follow-up (if applicable), 100-day safety follow-up, survival follow-up assessments at the visits according to Table 7-1 and Table 7-1b and should not be considered withdrawn from the study.

If a study withdrawal occurs, or if the patient fails to return for visits, the Investigator must make every effort (e.g. telephone, email, letter) to determine the primary reason for a patient's premature withdrawal from the study, and record this information on the End of Treatment Disposition CRF page.

If a patient discontinues study treatment, but continues study assessments (i.e. enters post-treatment follow-up phase), the patient remains on study until such time as he/she completes protocol criteria for ending study assessments (i.e. ending post-treatment follow-up phase). At that time (ending post-treatment follow-up phase), the reason for study completion should be recorded on the End of Post Treatment Phase Disposition CRF page.

In exceptional cases patients may remain on study treatment or re-initiate study treatment even after meeting a criterion for premature patient withdrawal if a clear benefit to the patient can be documented and there is agreement between Investigator and Novartis.

Patients who transfer into a Novartis roll-over study or an alternative treatment option to continue provision of study treatment will perform the end of treatment procedures.

7.1.4.1 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study any longer, and
- Does not allow further collection of personal data

[redacted]

In this situation, the investigator should make a reasonable effort (e.g. telephone, email, letter) to understand the primary reason for patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.4.2 Criteria for premature patient withdrawal

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Patients may be withdrawn from the study if any of the following occur:

- AE
- Lost to follow-up
- Physician decision
- Progressive disease
- Protocol deviation
- Study terminated by the sponsor
- Patient withdrew consent

Patients will be withdrawn from the study if any of the following occur:

- Pregnancy

[redacted]

- Death

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.1.4.2. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.6.

7.1.4.3 Replacement policy

No replacements will be needed.

7.1.5 Follow up period

100-day safety follow-up period

All patients must have safety evaluations as per Table 7-1 and Table 7-1b for 100 days after the last dose of investigational drug(s), even if a new anti-cancer therapy is initiated.

Hematological and chemistry assessments should be done in person at 30-day and 100-day follow up visits as per Table 7-1. Following the approval of protocol amendment 08, it is not required to perform these assessments as per Table 7-1b.

All patients will be followed for AEs for 100 days after the last dose of the study drug.

Information related to AEs (including concomitant medications taken for ongoing AEs) and ongoing anti-neoplastic treatments will be collected for 100 days after last dose of study drug. All AEs suspected to be related to study treatment should be followed up weekly, or as clinically indicated, until resolution or stabilization. Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Disease progression follow up

All patients enrolled in the study who discontinue study treatment for any reason other than disease progression will have a tumor assessment every 12 weeks (± 7 days) as detailed in Table 7-1 and Table 7-1b, until disease progression or the initiation of subsequent anticancer therapies, death, or 12 months has elapsed from last patient first treatment, whichever occurs first. Any newly started antineoplastic therapies during the follow-up period must be recorded on the antineoplastic therapy since discontinuation eCRF.

Survival follow-up period

All patients enrolled in the study will be followed by phone call for survival every 12 weeks for one year after discontinuation of treatment until death, lost to follow up, consent withdrawal, or end of study (see Section 4.3), whichever occurs first. Newly started antineoplastic therapies during this follow-up period must be recorded on the Antineoplastic therapy eCRF since discontinuation.

[redacted]

For patients who transfer to a Novartis roll-over study or an alternative treatment option to continue provision of study treatment, the follow-up for safety, disease progression and survival will not be performed.

7.1.6 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be determined locally according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 4). The local investigator's assessment will be used for the primary endpoint analysis and for treatment decision making.

CT/MRI scans will be performed at baseline within 28 days (preferably 7 days) before start of treatment and subsequently every 8 weeks up to cycle 12, every 12 weeks (as per regional and/or institutional standards) from Cycle 13 to Cycle 24, every 24 weeks from Cycle 25 to Cycle 36, and every 52 weeks from Cycle 37, until progression of disease. For patients who enter the follow-up period after completing 13 or more cycles of therapy, radiological assessment will be performed every 12 weeks. Following the approval of protocol amendment 08 and after 12 months has elapsed since last patient first treatment, no efficacy assessment will be performed on the still ongoing patients and patients in disease progression follow-up. If there is an event of unconfirmed PR at this time point, an additional radiological assessment will be performed to confirm the response. See Table 7-2 for details. If the prior tumor evaluation was done within 28 days of EOT or objective evidence of progressive disease has already been documented, then tumor evaluations do not need to be repeated at EOT. Depending on regulatory requirements the EOT scan may be performed within an extended time frame but not later than 8 weeks from the last CT/MRI scan.

Disease progression follow-up should be performed as described in Section 7.1.5. After baseline, all assessments should be performed within ±7 days of the scheduled day of assessment. Imaging evaluations subsequent to an off-schedule confirmatory scan should be performed according to the original assessment schedule. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow up.

If at baseline a patient has a medical contraindication to CT i.v. contrast or develops a contraindication during the trial, a non-contrast CT of chest plus contrast-enhanced MRI of abdomen is acceptable.

[redacted]

Patients with clinical evidence of bone metastases must have a whole body bone scan at baseline per local institutional practice (e.g., Tc99m bone scan, NaF positron emission tomography (PET) or whole body bone MRI). Lesions identified on the whole body bone scan at baseline, which are not visible on the chest and abdomen CT (or MRI) scan should be imaged at baseline and followed at subsequent scheduled visits using localized CT, MRI or X-ray. After baseline, whole body bone scans need not be repeated, unless clinically indicated.

Skin lesions present at baseline should be documented using color photography, including a ruler, so that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening.

Baseline brain CT or MRI will be mandated for all patients prior to study treatment. Subsequent brain scans should only be conducted if brain lesions are documented at baseline for eligible patients or in patients that develop symptoms indicative of brain metastases.

All CRs and PRs must be confirmed by a second assessment not earlier than 4 weeks after the criteria for response are first met.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media.

All patients discontinuing from the study for PD must have their disease progression documented by radiologic evaluation. In cases of clinically-evident disease progression, all efforts should be made to perform a radiologic evaluation. Following the approval of protocol amendment 08 and after 12 months has elapsed since last patient first treatment, CT/MRI scans for routine disease monitoring purposes may be performed following local standard of care outside the setting of this study.

Patients with symptoms of rapidly progressing disease without radiological evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to ‘Disease progression’ or death due to study indication.

All radiological assessments obtained for patients will be centrally collected and subjected to quality checks by an imaging CRO selected by Novartis. The site manual provided by the designated imaging CRO will provide further details regarding image collection.

[redacted]

Table 7-2 Imaging or disease assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up*
CT or MRI with contrast enhancement (Chest and Abdomen)	Mandated	Mandated, every 8 weeks (±7 days) up to cycle 12 Every 12 weeks (±7 days) from Cycle 13 Day 1 to Cycle 24, every 24 weeks (±7 days) from Cycle 25 to Cycle 36, every 52 weeks (±7 days) from Cycle 37; every 12 weeks (+/- 7 days) during follow up for patients discontinuing for reasons other than disease progression.
Whole body bone scan	If clinically indicated	If clinically indicated
Brain CT or MRI	Mandated	If brain lesions at screening every 8 weeks (±7 days) up to cycle 12. Every 12 weeks (±7 days) from Cycle 13 Day 1 to Cycle 24, every 24 weeks (±7 days) from Cycle 25 to Cycle 36, every 52 weeks (±7 days) from Cycle 37; every 12 weeks (+/- 7 days) during follow up for patients discontinuing for reasons other than disease progression.
Bone X-ray, CT or MRI (bone lesions only)	If lesions on bone scan that are not visible on the chest and abdomen CT/MRI	If bone lesions at screening every 8 weeks (±7 days) up to cycle 12. Every 12 weeks (±7 days) from Cycle 13 Day 1 to Cycle 24, every 24 weeks (±7 days) from Cycle 25 to Cycle 36, every 52 weeks (±7 days) from Cycle 37; every 12 weeks (+/- 7 days) during follow up for patients discontinuing for reasons other than disease progression.
Skin color photography (skin lesions only)	Mandated if skin lesions at screening	If skin lesions at screening every 8 weeks (±7 days) up to cycle 12. Every 12 weeks (±7 days) from Cycle 13 Day 1; every 12 weeks (+/- 7 days) during follow up for patients discontinuing for reasons other than disease progression.
CT or MRI of other tumor sites (e.g., pelvis)	If clinically indicated	If lesions identified at screening every 8 weeks (±7 days) up to cycle 12. Every 12 weeks (±7 days) from Cycle 13 Day 1 to Cycle 24, every 24 weeks (±7 days) from Cycle 25 to Cycle 36, every 52 weeks (±7 days) from Cycle 37; every 12 weeks (+/- 7 days) during follow up for patients discontinuing for reasons other than disease progression.
* Following the approval of protocol amendment 08, no efficacy assessment will be performed on the still ongoing patients and patients in disease progression follow-up after 12 months has elapsed since last patient first treatment.		

CT: Chest, abdomen and pelvis CT. The preferred radiologic technique is CT with intravenous (i.v.) contrast. However, if CT assessments require additional regulatory approval in a country,

[redacted]

MRI is allowed for chest, abdomen and pelvis. If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

Bone scintigraphy: If bone metastases are suspected/clinically indicated, a whole body bone scan per institutional standard of care. Localized CT, MRI or X-rays should be acquired for all skeletal lesions identified on bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI/X-ray. These lesions, which are not visible on chest, abdomen and pelvis CT/MRI/X-ray, should be evaluated with same frequency as chest, abdomen, pelvis CT/MRI/X-ray.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing the procedures listed below as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination that evaluates all major organ systems will be performed at screening/baseline. Subsequent physical exams may be limited and should be focused on sites of disease to explore clinical signs and symptoms.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure, pulse oximetry) must be performed before dosing and as indicated in Table 7-1 and Table 7-1b as per institutional standards.

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured as indicated in Table 7-1.

Height information will be collected at screening only. Following the approval of protocol amendment 08, it is not required to collect weight information as per Table 7-1b.

7.2.2.4 Performance status

ECOG performance status will be assessed according to Table 7-1 and Table 7-3. Following the approval of protocol amendment 08, it is not required to collect ECOG performance status as per Table 7-1b.

[redacted]

Table 7-3 ECOG performance status

Grade	ECOG Status
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

7.2.2.5 Laboratory evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally, at the site. Refer to Table 7-4 and Table 7-4b for a summary of the parameters to be evaluated according to Table 7-1 and Table 7-1b.

Unscheduled assessment can be performed if clinically indicated.

Novartis will be provided with a copy of the site's local laboratory certification and tabulation of the normal ranges for each parameter required at study start and should be kept up to date on an ongoing basis. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Table 7-4 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, platelets, white blood cells (WBC), WBC morphology with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), amylase, lipase, calcium, chloride, magnesium, potassium, creatinine, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, blood urea nitrogen (BUN) or urea, uric acid, glucose, Thyroid functions tests (freeT3, freeT4, TSH), Hepatitis B (HBsAg, HBsAb, and HBcAb; if HBsAb positive; Hep B DNA needs to be performed) at screening and Hepatitis C (HC Ab and HC-RNA) at screening only. Please see Appendix 6 for additional guidelines), HIV test (screening only for patients in Germany)
Coagulation	Prothrombin time (PT) or international normalized ratio (INR)

Table 7-4b Local clinical laboratory parameters collection plan (effective after protocol amendment 08 is approved)

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, platelets, white blood cells (WBC)
Chemistry	Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), amylase, lipase, creatinine, total bilirubin, thyroid functions tests (freeT4 & TSH)

[redacted]

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1. Following the approval of protocol amendment 08, please follow the assessment plan in Table 7-1b and Table 7-4b.

7.2.2.5.2 Clinical chemistry

Clinical chemistry panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1. Following the approval of protocol amendment 08, please follow the assessment plan in Table 7-1b and Table 7-4b.

7.2.2.5.3 Coagulation

Coagulation panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1 and Table 7-1b.

7.2.2.5.4 Pregnancy and assessments of fertility

Serum pregnancy test will be performed at screening, C1D1, at day 1 of subsequent cycles, at the end of treatment visit and at the 30-day safety follow up visit. Monthly urine pregnancy tests should be performed thereafter until approximately 23 weeks after discontinuation of the study medication. Urine pregnancy test results should remain with the patient records and do not need to be included into the clinical database.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as per the assessment schedule in Table 7-1, Table 7-1b and Table 7-5.

Table 7-5 Central ECG collection plan

Cycles	Day	Time Point
Screening [a]	-28 to -1	Anytime
Cycle 1	1	Pre-dose
Cycle 1	15	Pre-dose
Cycle 1[b]	15	3 hr post dose (+/- 30 min)
Cycle 2 and afterwards	1	Pre-dose
EOT	-	Anytime
Unscheduled		Anytime

[a.] A single standard 12 lead ECG will be performed at screening. Triplicate ECGs will be done at all other time points.

[b.] This time point is only needed for safety monitoring cohort patients following EGF816 or INC280

Note: If both ECG and PK sample are scheduled at the same time, the PK sample should be taken immediately within 1 hour) after ECG assessment

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where

[redacted]

regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

Triplicate ECGs will be performed at least 5 minutes apart. All ECGs will be independently reviewed by a central laboratory. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the laboratory manual. Following the approval of protocol amendment 08, it is not required to transmit ECG for central review.

7.2.3 Pharmacokinetics

Serial blood samples will be collected from all patients in the safety cohort for the analysis of INC280, EGF816, and Nivolumab concentration. The PK analysis will be performed according to Section 10.5.3. Following the approval of protocol amendment 08, no additional PK and immunogenicity samples will be collected from the still ongoing patients.

[redacted]

7.2.3.1 Pharmacokinetic blood sample collection and handling

The exact date and clock times of drug administration and PK blood draw will be recorded on the appropriate eCRF. The timing of meals, before and after the dose on days when PK samples are drawn, should be recorded on the eCRF. If vomiting occurs within 4 hours following INC280 and EGF816 administration on the day of post dose PK blood sampling, the clock time of vomiting should be recorded on the Dose Administration Record PK eCRF page.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein opposite to the arm used for infusion. Refer to the CEGF816X2201C Laboratory Manual for detailed instructions for the collection, handling, and shipment of PK samples.

7.2.3.2 Pharmacokinetic and immunogenicity sampling schedule

For safety monitoring cohort, blood samples for PK profile will be collected for INC280 and EGF816 on Cycle 1 Day 15. In addition, blood samples for trough concentration will be collected for EGF816, INC280 and Nivolumab in order to obtain steady state exposure for all patients for exploring exposure-response or exposure-toxicity when necessary. If patient experiences an AE that fits the criteria of a SAE as determined by the Investigator, an unscheduled PK blood sample should be collected for the measurement of INC280 or, EGF816 and Nivolumab drug concentrations.

Blood samples for Nivolumab immunogenicity analysis will be collected according to schedule given in Table 7-8. Samples will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemilumeminescent (ECL) immunoassay.

[redacted]

Table 7-6 Schedule of blood collection for EGF816 (QD), PK for patients participating in the safety monitoring cohort

Cycle	Day	Scheduled time (hours)	Dose reference ID	Sample number
1	1	Pre-C1D1 dose [a]	1	1
1	8	Pre-C1D8 dose [a]	2/102	2
1	15	0 hr/ Pre- C1D15 dose [a]	3/103	3
1	15	1 hr (±10 minutes)	3	4
1	15	3 hr (±15 minutes)	3	5
1	15	6 hr (±1 hr)	3	6
1	15	8 hr (±2 hr)	3	7
2	1	0 hr /Pre-C2D1 dose [a]	4/104	8
4	1	0 hr /pre-C4D1 dose [a]	5/105	9
6	1	0 hr/ pre-C6D1 dose [a]	6/106	10
8	1	0 hr/ pre-C8D1 dose [a]	7/107	11
		Unscheduled and at the time of progression [b]		1001+

a. Take samples immediately prior to the administration of EGF816
b. Unscheduled blood samples will be uniquely, sequentially numbered 1001, 1002,

Table 7-7 Schedule of blood collection for INC280 (BID) PK for patients participating in the safety monitoring cohort

Cycle	Day	Scheduled time (hours)	Dose reference ID	Sample number
1	15	0 hr / pre-C1D15 AM dose [a]	21/211	201
1	15	1 hr (±10 minutes)	21	202
1	15	3 hr (±15 minutes)	21	203
1	15	6 hr (±1 hr)	21	204
1	15	8 hr (±2 hr)	21	205
2	1	0 hr / pre-C2D1 AM dose [a]	22/221	206
4	1	0 hr / pre-C4D1 AM dose [a]	23/231	207
6	1	0 hr / pre-C6D1 AM dose [a]	24/241	208
8	1	0 hr / pre-C8D1 AM dose [a]	25/251	209
NA	NA	Unscheduled and at the time of progression [b]	--	2001+ [b]

a. Take samples immediately prior to the administration of INC280
b. Unscheduled blood samples will be uniquely, sequentially numbered 2001, 2002,

[redacted]

Table 7-8 Schedule of blood collection for Nivolumab (1 hour infusion) PK and immunogenicity for all patients

Cycle	Day	Scheduled time (hours) [c]	Description	Dose reference ID	Sample number
1	1	0 hr	Preinfusion [a]	40	400
1	15	0 hr	Preinfusion [a]	40/41	401
2	1	0 hr	Preinfusion [a]	41/42	402
4	1	0 hr	Preinfusion [a]	43/431	403
8	1	0 hr	Preinfusion [a]	44/441	404
Every 8th Cycle after C8D1 until discontinuation of study treatment (2 follow up visits up to 100 days from end of treatment)	1	0 hr	Preinfusion [a]	45 [e]/451	405 [d]
NA	NA		Unscheduled and at the time of progression [b]	--	4001+ [b]

a. Take samples within 60 min before the 1hr infusion begins
b. Unscheduled blood samples will be uniquely, sequentially numbered 4001, 4002,
c. Time is relative to the beginning of the infusion
d. Sample number will be labeled sequentially from 405, 406, ….until the 2 follow-up visit samples are collected (samples for the follow-up visit can be collected anytime during the visit)
e. Dose reference ID will be labeled sequentially from 45, 46, ….until the 2 follow-up visit samples are collected (samples for the follow-up visit can be collected anytime during the visit)

Table 7-9 Schedule of blood collection for EGF816 (QD) PK for patients NOT participating in the safety monitoring cohort

Cycle	Day	Scheduled time (hours)	Dose reference ID	Sample number
1	15	0 hr/ Pre- C1D15 dose [a]	3/103	3
2	1	0 hr /Pre-C2D1 dose [a]	4/104	8
4	1	0 hr /pre-C4D1 dose [a]	5/105	9
6	1	0 hr/ pre-C6D1 dose [a]	6/106	10
8	1	0 hr/ pre-C8D1 dose [a]	7/107	11
		Unscheduled and at the time of progression [b]		1001+

a. Take samples immediately prior to the administration of EGF816
b. Unscheduled blood samples will be uniquely, sequentially numbered 1001, 1002,

[redacted]

Table 7-10 Schedule of blood collection for INC280 (BID) PK for patients NOT participating in the safety monitoring cohort

Cycle	Day	Scheduled time (hours)	Dose reference ID	Sample number
1	15	0 hr / pre-C1D15 AM dose [a]	21/211	201
2	1	0 hr / pre-C2D1 AM dose [a]	22/221	206
4	1	0 hr / pre-C4D1 AM dose [a]	23/231	207
6	1	0 hr / pre-C6D1 AM dose [a]	24/241	208
8	1	0 hr / pre-C8D1 AM dose [a]	25/251	209
NA	NA	Unscheduled and at the time of progression [b]	--	2001+ [b]

Take samples immediately prior to the administration of INC280
Unscheduled blood samples will be uniquely, sequentially numbered 2001, 2002,

7.2.3.3 Analytical method

INC280 and EGF816 concentrations in human plasma will be determined with a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Nivolumab concentrations in human serum will be determined with a validated ELISA assay. Any results below the lower limit of quantification (LLOQ) and any missing samples will be labeled accordingly.

7.2.4 Biomarkers

The biomarker collections for this study are summarized in Table 7-11.

While the goal of the biomarkers is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection and analysis may be omitted at the discretion of Novartis.

[redacted]

Table 7-11 Biomarker sample collection

Sample Type	Analyses	Collection Visit Schedule
Archival tumor sample along with a corresponding pathology report Or Newly obtained tumor biopsy sample[3]	EGFR mutation T790M[1] (Group 1 patients only) cMet status[1] (Group 2 patients only)	Molecular Pre-screening (required)
Newly obtained tumor biopsy sample[2,4]	cMet mutation testing (screening/baseline sample only)	Screening[4]

1. Please also refer to Section 7.1.1.
2. [redacted]
3. For US patients cMet detection will be performed on archival tumor samples only
4. An archival sample with a corresponding pathology report may be substituted if it has been recently obtained with no intervening systemic anti-neoplastic treatment, and after documented discussion with Novartis. See Section 7.2.4.1.

7.2.4.1 Biomarker tumor assessment

In this study biomarker analyses will be used to investigate the effect of the investigational agents as well as to determine how changes in the markers may relate to exposure and clinical outcomes. The sample collection information as required should be recorded on the eCRF page(s) and central laboratory requisition form(s).

[redacted]

[redacted]

Additionally, if submitting an archival block, an accompanying pathology report must be submitted. Additional archival tumor specimen(s) may be requested if the initial sample submitted is insufficient to complete the planned analyses.

[redacted]

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Patients will sign the molecular pre-screening ICF to undergo tests for EGFR mutation and cMet status. AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Serious Adverse event monitoring should be continued for at least 100 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study but is collected as a seriousness criterion; rather, information about deaths will be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)

[redacted]

2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST 1.1 Appendix 4, should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

If a clinical sample is obtained as part of the evaluation of an adverse event that is suspected to be treatment-related (e.g., skin biopsy for rash), Novartis may request that the remaining clinical sample be submitted for central evaluation to gain further understanding of that adverse event, or other safety findings associated with that adverse event.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per

[redacted]

investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event
- Serious adverse events considered by the investigator to be possibly related to a biopsy procedure will be indicated as such in the AE CRF.

8.2.2 Reporting

For patients with unknown EGFR and/or cMet statuses and who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). Serious adverse events considered to be possibly related to a biopsy procedure will be indicated as such in the Adverse Event eCRF. SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30-days after the last study related procedure.

For patients with known EGFR and/or cMet statuses who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

[redacted]

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 100 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 100 days period (or 5 half-lives, whichever is longer) should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours Novartis. Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

A copy of the SAE data submitted must be kept with the case report form documentation at the study site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment or within 23 weeks of discontinuing study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the

[redacted]

possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Outcomes of pregnancies in female partners of any males who took study treatment in this study, occurring while the male partner is on study treatment or within 31 weeks of discontinuing study treatment, should be collected. The newborn will be followed up to three months after delivery date. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be in place for this trial. However, measures are put in place for monitoring the safety of the patients participating in the study, and Novartis will convene a joint teleconference with the participating Investigators to ensure a prompt review of safety data and constant monitoring for emerging safety signals by participating study sites and Novartis Personnel. As for any other study conducted by Novartis, any SUSAR and/or new safety signals will be promptly communicated to all participating investigators and Health Authorities.

When patients in the safety monitoring cohort have completed six weeks of treatment or discontinued earlier, Novartis and investigators will have a safety assessment meeting to qualitatively review clinical, PK and laboratory data and to decide on the appropriate dose for study continuation (Section 2.2 and Section 4.1).

Individual patient data will be reviewed on an ongoing basis and aggregate safety data and the primary endpoint will be monitored quarterly by the study team across the duration of the trial. The data review and analysis will be based on the available investigator reported data in the clinical database at the respective time.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

[redacted]

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they

[redacted]

have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

Blood and tumor samples for PK and biomarkers will be collected by sites and sent to a Central laboratory for processing. The Laboratory results will be sent electronically to Novartis. Radiological and photography data will be acquired by the sites and interpreted locally. Imaging data will be centrally collected and checked for quality by an imaging CRO designated by Novartis and may undergo independent review according to the Novartis guideline. Details regarding all CRO procedures including collection and shipment of data will be described in the manual provided by the respective CRO.

If a patient enrolls on a companion sample collection study to evaluate the mechanisms of resistance, data required for the companion sample collection study are collected in the clinical trial database for the treatment protocol. A description of the data to be collected for the study of resistance is provided in the companion sample collection protocol.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Biomarker and PK samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Study data will be analyzed by Novartis and/or designated contract research organization (CRO). Any data analysis carried out independently by the investigator must be submitted to Novartis before publication or presentation.

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetics and pharmacodynamics measurements. Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data summary statistics including mean, standard deviation, median, minimum, and maximum will be presented. In addition, individual listings of all raw data captured in the clinical database will be presented

[redacted]

by treatment group and patient. All data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis.

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.

The primary analysis will be conducted after a minimum of 12 months has elapsed since last patient first treatment. This analysis will consist of the results related to the primary and secondary endpoints, and will include all the available data. Any additional data collected after the data cutoff date for the primary analysis will be further summarized and reported in a final study report once the end of study is reached as defined in Section 4.3.

10.1 Analysis sets

The following analysis sets which will be derived prior to database lock will be used.

10.1.1 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. The FAS will be used for all listings of raw data.

10.1.2 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. A precise definition of "actually received" will be added in the Reporting and Analysis Plan (RAP).

10.1.3 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 as per Appendix 4.
- 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.

[redacted]

- **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 (see Section 10.4). If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively by treatment group for the FAS. For patients from Germany HIV test results will be listed by treatment group.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

Duration of exposure to study treatment in days, as well as actual total doses, actual dose intensities, and relative dose intensities of both study drugs will be summarized using descriptive statistics by treatment group for the safety set.

10.3.2 Concomitant medications

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized by treatment group for the safety set by ATC (Anatomical therapeutic chemical classification system) term.

10.3.3 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

10.4 Primary objective

The primary objective is to estimate the clinical activity of Nivolumab in combination with EGF816 or INC280 (Table 3-1).

10.4.1 Variable

The primary efficacy variable is PFS rate assessed at 6 months (more precisely after 6 cycles = 168 days as specified in Table 3-1) 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 (see Appendix 4).

[redacted]

The primary analysis will be performed after 12 months has elapsed from last patient first treatment.

10.4.2 Statistical hypothesis, model, and method of analysis

For each treatment group a Bayesian design will be used (see Appendix 3 for details). PFS will be modeled using a Weibull distribution. 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.

The primary Bayesian analysis of ORR will only be performed for the final selected dose levels. Other secondary analyses of activity will be performed for all treatment groups as described in Section 10.5.2.

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 estimated 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 estimated 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

[redacted]

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 estimated 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.

10.4.3 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.

10.4.4 Supportive analyses

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 and details of the analyses will be defined in the Reporting and Analysis Plan (RAP).

10.5 Secondary objectives

Please refer to Table 3-1 for secondary objectives

10.5.1 Safety objectives

10.5.1.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used if not otherwise specified. All listings and tables will be presented by treatment group. 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.

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

[redacted]

10.5.1.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), relation to study treatment by treatment group.

Deaths reportable as serious adverse events (SAEs) and non-fatal SAEs will be listed by patient and tabulated by treatment group.

10.5.1.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4 (see below for details)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the MAP and/or RAP.

10.5.1.4 Other safety data

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

[redacted]

10.5.1.5 Tolerability

Tolerability of study drugs will be assessed by summarizing the frequency of dose interruption, frequency of dose reduction, and dose intensity. Reasons for dose interruption and dose reduction will be listed by patient and summarized.

10.5.2 Efficacy objectives

The secondary efficacy objectives are to evaluate 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 and PFS will be defined as per RECIST v1.1 (see Appendix 4). 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 and the Bayesian approach as for the primary endpoint. 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.

10.5.3 Pharmacokinetics

The FAS will be used in all pharmacokinetic data analysis and PK summary statistics. 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. Zero concentrations will not be included in the geometric mean calculation. Individual concentration-time profile as well as mean concentration-time profile will be plotted.

PK parameters will be determined for all PK-evaluable patients with non-compartmental method(s) using Phoenix WinNonlin version 6.2 or above (Pharsight, Mountain View, CA). [redacted] Derived PK parameters, including but not limited to those listed in Table 10-1, will be summarized with descriptive statistics, including arithmetic and geometric mean, median, standard deviation, CV, geometric CV, minimum and maximum. Only median values and ranges will be given for Tmax. Missing data will not be imputed.

[redacted]

[redacted]

Table 10-1 Noncompartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUC0-t	The AUC from time zero to t hours after administration (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)

10.5.3.1 Data handling principles

Missing concentration values will be reported as is in data listings. Concentration values of INC280, EGF816 and Nivolumab below the respective Lower Limit of Quantitation (LLOQ, BLLOQ) will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

[redacted]

10.7 Interim analysis

No interim analysis will be conducted. However, individual patient data will be reviewed on an ongoing basis by the study team across the duration of the trial (Section 8.5). When patients in the safety monitoring cohort have completed six weeks treatment or discontinued earlier, Novartis and principal investigators will have a safety assessment meeting to review clinical, PK and laboratory data and to decide on the dose for study continuation (Section 2.2 and Section 4.1).

10.8 Sample size calculation

The statistical set-up is described in Section 10.4.2 and details about operating characteristics are described in 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:

[redacted]

- 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.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local

[redacted]

regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

[redacted]

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

[redacted]

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility,

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and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB

[redacted]

approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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14 Appendices

Table 14-1 and Table 14-2 present concomitant medications by mechanism of interaction. Some drugs are, as they have an interaction potential through several mechanisms, presented in both tables. If a medication is listed in both Table 14-1 and Table 14-2, the more stringent practice shall be applied (that is, the medication shall be prohibited as in Table 14-2).

14.1 Appendix 1: List of concomitant medications to be used with caution

Table 14-1 Permitted concomitant medications requiring caution

Mechanism of Interaction	Drug Name
Strong CYP3A4 inhibitor**	clarithromycin, telithromycin, troleandomycin, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, itraconazole, ketoconazole, posaconazole, voriconazole, boceprevir, telaprevir, cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone, grapefruit, grapefruit juice, grapefruit hybrids, danoprevir/ritonavir, eltegravir/ritonavir
Moderate CYP3A4 inhibitor*	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, imatinib, lomitapide, netupitant, nilotinib, schisandra sphenanthera, tofisopam, verapamil
Moderate CYP3A4 inducer***	bosentan, efavirenz, etravirine, genistein, lersivirine, lopinavir, modafinil, nafcillin, semagacestat, talviraline, thioridazine tipranavir
CYP1A2 substrate with NTI**	theophylline, tizanidine
CYP2C9 substrate with NTI**	Phenytoin, warfarin
CYP2C19 substrate with NTI**	(S)-mephenytoin
Sensitive CYP2C8 substrate***	Repaglinide
Sensitive CYP2D6 substrate*	atomoxetine, bosentan, desipramine, doxepin, efavirenz, etravirine, encainide, genistein, methoxyphenamine, modafinil, nibivolol, nafcillin, nefazodone, perhexiline, perphenazine, risperidone, tolterodine, traxoprodil, trimipramine, tropisetron, [talviraline], vernakalant

[redacted]

Mechanism of Interaction	Drug Name
Sensitive CYP3A4 substrate**	vanafil, aronedarone, bosutinib, ebastine, brotizolam, ibrutinib, midazolam, triazolam, felodipine, nisoldipine, brecanavir, capravirine, darunavir, atorvastatin, lovastatin, simvastatin, everolimus, lurasidone, perospirone, quetiapine, levomethadyl, budesonide, fluticasone, sildenafil, vardenafil, aprepitant, casopitant, alpha-dihydroergocryptine, aplaviroc, buspirone, darifenacin, eletriptan, eplerenone, lumefantrine, maraviroc, ridaforolimus, ticagrelor, tolvaptan, vicriviroc, alfentanil, almorexant, atazanavir, conivaptan, danoprevir, dasatinib, elvitegravir, ibrutinib, indinavir, ivacaftor, lomitapide, lopinavir, midostaurin, neratinib, saquinavir, simeprevir, ticagrelor, terfenadine, tilidine, tipranavir, voclosporin
P-gp inhibitor*	alogliptin, amiodarone, azithromycin, canaglifozin, captopril, carvedilol, conivaptan, cremophor RH40, curcumin, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fluvoxamine, ginko, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lapatinib, lopinavir/ritonavir, mibefradil, milk thisle, mirabegron, nelfinavir, nifedipine, nitredipine, paroxetine, propafenone, quercetin, quinidine, ranolazine, rifampin, ritonavir, sequinavir/ritonavir, schisandra chinesis extract, simepravir, St. John's wort extract, talinolol, telaprevir, telmisartan, ticagrelor, tipranavir/ritonavir, tolvaptan, valspodar, vandetanib, verapamil, voclosporin
P-gp inducer*	avasimibe, carbamazepine, efavirenz, genistein, phenytoin, quercetin, rifampin, St. John's Wort extract
P-gp substrates**	Aliskiren, ambrisentan, atorvastatin, atorvastatin acid, azithromycin, cerivastatin, CP-481,715, cyclosporine, dabigatran, docetaxel, domperidone, doxorubicin, fentanyl, lapatinib, linezolid, loperamide, maraviroc, nevirapine, paclitaxel, proguanil, quinidine, ranolazine, ritonavir, saquinavir, simvastatin, sirolimus, sofosbuvir, tacrolimus, ticagrelor, voclosporin, colchicine, digoxin, everolimus, fexofenadine, , afatinib, alfuzosin, alogliptin, apixaban, apremilast, aprepitant, boceprevir, bosentan, carvedilol, carvedilol, caspofungin, ceritinib, citalopram, doxepin, eribulin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, levetiracetam, levofloxacin, linagliptin, losartan, maraviroc, mirabegron, moxifloxacin, naloxegol, nateglinide, nintedanib, olodaterol, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, quinine, riociguat, risperidone, rivaroxaban, silodosin, simeprevir, sitagliptin, sorafenib, telaprevir, tenofovir, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole.
P-gp substrate with NTI**	cyclosporine, digoxin, fentanyl, paclitaxel, phenytoin, quinidine, sirolimus, tacrolimus

[redacted]

Mechanism of Interaction	Drug Name
BCRP substrate***	atorvastatin daunorubicin, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, SN-38 (irinotecan), ethinylestradiol, simvastatin, sulfasalazine, sofosbuvir, topotecan, sulfasalazine
MATE substrate*	metformin, tenfovir
OATP substrates**	Atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, valsartan, olmesartan, telmisartan
**Proton pump inhibitor	Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole, dexlansoprazole
**Short acting gastric acid modulator and H2 receptor antagonist	Antacids containing aluminum hydroxide and magnesium hydroxide, or calcium carbonate cimetidine, famotidine, nizatidine, ranitidine

Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (v06 2016) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database.

The lists provided may not be exhaustive.

Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

* Applies to patients receiving EGF816 treatment

** Applies to patients receiving INC280 treatment

*** Applies to patients receiving either EGF816 or INC280 treatment

[redacted]

14.2 Appendix 2: Prohibited concomitant medications

Table 14-2 Prohibited concomitant medication

Mechanism of Interaction	Drug Name
Strong CYP3A4 inhibitor*	clarithromycin, telithromycin, troleandomycin indinavir, lopinavir, nelfinavir, ritonavir saquinavir, tipranavir/ ritonavir, itraconazole, ketoconazole, posaconazole, voriconazole boceprevir, telaprevir, danoprevir, cobicistat, conivaptan, mibefradil, nefazodone, grapefruit juice, grapefruit, grapefruit hybrids, danoprevir/ritonavir, eltegravir/ritonavir, indinavir/ritonavir, lopinavir/ritonavir (HIV), saquinavir/ritonavir
Strong CYP3A4 inducer***	avasimibe, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort, enzalutamide
Live vaccines*	e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines
Medications with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe**	amiodarone, anagrelide, arsenic trioxide, astemizole (off US mkt), azithromycin, bepridil (off US mkt), chloroquine, chlorpromazine, cisapride (off US mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US mkt), dronedarone, droperidol, erythromycin, escitalopram, flecainide, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off US mkt), mesoridazine (off US mkt), methadone, moxifloxacin, ondansetron, pentamidine, pimozide, probucol (off US mkt), procainamide (oral off US mkt), quinidine, sevoflurane, sotalol, sparfloxacin (off US mkt), sulpiride (not on US mkt), terfenadine (off US mkt), thioridazine, vandetanib For a comprehensive list of drugs, refer to www.qtdrugs.org
Immunosuppressive agents and Immunosuppressive doses of systemic corticosteroids (except when utilized to treat a drug related adverse event or as stated below) are prohibited. Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.	
Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (v06 2016, which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. The lists provided may not be exhaustive. Drugs between brackets are not marketed in US NTI: narrow therapeutic index NA, not available * Applies to patients receiving EGF816 treatment ** Applies to patients receiving INC280 treatment *** Applies to patients receiving either EGF816 or INC280 treatment	

14.3 Appendix 3: Bayesian study design set-up, posterior analysis and operating characteristics

All calculations below consider 1 month with 28 days, i.e. cycle duration.

14.3.1 Statistical model

For each treatment group a Bayesian design will be used to estimate PFS rate at 6 months and to provide inferential statements based on the uncertainty of this quantity. PFS time will be modeled using a Weibull distribution, which is a flexible distribution allowing for time varying hazard rate. The Weibull probability density function is given by

$$f(x) = \frac{\gamma}{\lambda}\left(\frac{x}{\lambda}\right)^{\gamma-1} exp\left[-\left(\frac{x}{\lambda}\right)^{\gamma}\right], \qquad x \geq 0, \qquad [1]$$

where γ is a shape parameter and λ a scale parameter. The corresponding survival function is

$$S(x) = exp\left[-\left(\frac{x}{\lambda}\right)^{\gamma}\right], \qquad [2]$$

and the median PFS can be calculated as

$$x_{median} = \lambda \sqrt[\gamma]{\ln(2)}. \qquad [3]$$

14.3.2 Prior specifications

For each treatment group it is assumed that the prior distribution of γ is an exponential distribution with a specified rate and that the prior distribution of the natural log of λ, ln(λ), is a normal distribution with specified mean and standard deviation. The prior distribution of PFS rate at 6 months is estimated by simulations with the following steps:

1. Draw 100000 random samples of γ from the specified exponential distribution and 100000 random samples of ln(λ) from the specified normal distribution.
2. Calculate PFS rates at 6 months using equation [2] with x=6 and the 100000 pairs of γ and λ.
3. Calculate mean of the 100000 PFS rates at 6 months, proportion of values in the unacceptable activity interval, and proportion of values equal to or greater than the indifference point, i.e. clinically relevant activity.

The rate for γ prior distribution and the mean and standard deviation for ln(λ) prior distribution are chosen to give a prior distribution of PFS rate at 6 months that has a mean close to the respective indifference point and is reasonably non-informative with a nontrivial probability for unacceptable activity in the left tail and a nontrivial probability for clinically relevant activity in the right tail. The selected prior parameter values and the resulting prior distributions of PFS rate at 6 months are summarized in Table 14-3 below.

[redacted]

Table 14-3 Specifications for prior distributions

Group	Prior parameter			Prior distribution of PFS rate at 6 months		
	Rate for γ	Mean for ln(λ)	SD for ln(λ)	Mean	Prob. unacceptable activity	Prob. clin. relevant activity
1) Nivolumab & EGF816	0.5	3	1	69%	0.33 in [0%, 55%)	0.54 in [70%, 100%]
2) Nivolumab & INC280 (Sub-group A)	2.0	3	2.25	50%	0.25 in [0%, 35%)	0.43 in [50%, 100%]
3) Nivolumab & INC280 (Sub-group B)	5	2.3	5	40%	0.24 in [0%, 25%)	0.43 in [40%, 100%]

14.3.3 Operating characteristics

The posterior distribution of PFS rate at 6 months is not recognizable and an analytical solution does not exist. The operating characteristics for the Bayesian analysis described above are obtained by performing extensive simulations

14.3.3.1 Generating hypothetical datasets

Let n_i and a_i denote the sample size and average accrual rate per month of treatment group i. The values of n_i and a_i are specified below:

Treatment group (i)	Sample size (n_i)	Average accrual rate (a_i)
Group 1	40	6.5
Group 2 Sub-group A	20	1.0
Group 2 Sub-group B	30	2.0

For each patient within a treatment group the following variables are calculated:

- Accrual waiting time: It is assumed that the accrual waiting time of Cycle 1 Day 1 between two consecutive patients follows an exponential distribution with a rate of a_i. The accrual waiting time is in unit of month and set to 0 for the first patient.
- Accrual calendar time: This is the cumulative sum of the accrual waiting times. The origin is set to 0 at Cycle 1 Day 1 of the first patient. The interval from the origin to Cycle 1 Day 1 of the last patient is accrual duration.
- End of study calendar time (EOS): It is set at Cycle 1 Day 1 of the last patient plus 6 months. This is also the study duration.
- PFS time: It is assumed that the PFS time in unit of month follows an exponential distribution with a rate of -ln(specified true PFS rate at 6 months) / 6. The origin is Cycle 1 Day 1 of each patient.
- PFS calendar time: This is the sum of accrual calendar time and PFS time. The origin is Cycle 1 Day 1 of the first patient.
- Censoring time: The risk of censoring not due to cut-off for primary CSR is set at 0.15 per patient-year (i.e. 365 days). It is assumed that the censoring time in unit of month follows

[redacted]

an exponential distribution with a rate of -ln(1 - 0.15) / (365/28) ≅0.012. The origin is Cycle 1 Day 1 of each patient.

- Censoring calendar time: This is the sum of accrual calendar time and censoring time. The origin is Cycle 1 Day 1 of the first patient.
- Event indicator: If the PFS time is smaller than the censoring time and PFS calendar time is smaller than EOS, then the PFS event is observed; otherwise PFS is censored.
- Observation time: For a PFS event the observation time is the respective PFS time. For a censored case the observation time is the respective censoring time if censoring calendar time is smaller than EOS, or equals (EOS - accrual calendar time) otherwise. The origin is Cycle 1 Day 1 of each patient.

For each treatment group several possible values for true PFS rate at 6 months are specified. For each scenario with one of the specified values for true PFS rate at 6 months the hypothetical PFS dataset is generated by the following steps:

1. Set accrual waiting time to 0 for the first patient. Generate a random sample of accrual waiting times for the remaining $n_i - 1$ patients from an exponential distribution with the rate of a_i.
2. Generate a random sample of n_i PFS times from an exponential distribution with the rate of -ln(specified true PFS rate at 6 months) / 6.
3. Generate a random sample of n_i censoring times from an exponential distribution with the rate of -ln(1 -0.15) / (365/28).
4. Calculate accrual calendar time, EOS, PFS calendar time and censoring calendar time to determine event indicator and observation time for each patient.

The steps 1-4 above are repeated to generate a total of 1000 hypothetical datasets for each scenario.

14.3.3.2 Posterior analysis

Primary endpoint

Given the prior distributions and parameter values specified in Section 14.3.2 above, the corresponding posterior distributions of γ and $\ln(\lambda)$ for each of the 1000 hypothetical datasets are obtained by performing extensive MCMC simulations using R and WinBUGS software packages, with 5000 iterations for each of 4 chains. For each pair of posterior values of γ and $\ln(\lambda)$ the PFS rate at 6 months is calculated using equation [2] with x=6. The calculated PFS rates at 6 months from the iterations form the posterior distribution for the primary endpoint. The mean, median, standard deviation and 95% credible intervals for PFS rates at 6 months will be calculated from this posterior distribution. The posterior mean is taken as the estimated PFS rate at 6 months. The posterior risk of being in a specific interval is calculated as the proportion of calculated PFS rate at 6 months in that specific interval.

For Group 1: If the estimated 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 0.05, then preliminary anti-tumor activity of the study treatment will be declared, i.e. success. The operating characteristics in terms of probability of success among 1000 hypothetical

[redacted]

datasets for the above-mentioned Bayesian study design under different true PFS rates at 6 months are summarized in Table 14-4 below. Such operating characteristics are satisfactory.

Table 14-4 Operating characteristics of Group 1 Bayesian study design

True PFS rate at 6 months	55%	70%	75%	80%	85%
Probability of success	0.02	0.53	0.81	0.96	1

In Sub-group A if the estimated 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 0.05, then preliminary anti-tumor activity of the study treatment will be declared, i.e. success. In Sub-group B if the estimated 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 0.05, then preliminary anti-tumor activity of the study treatment will be declared, i.e. success.

The operating characteristics in terms of probability of success among 1000 hypothetical datasets for the above-mentioned Bayesian study design under different true PFS rates at 6 months are summarized in Table 14-5 below. Such operating characteristics are satisfactory.

Table 14-5 Operating characteristics of Group 2 Bayesian study design

Sub-group A:					
True PFS rate at 6 months	35%	50%	55%	60%	65%
Probability of success	0.05	0.50	0.73	0.87	0.95
Sub-group B:					
True PFS rate at 6 months	25%	40%	45%	50%	55%
Probability of success	0.02	0.59	0.80	0.93	0.98

Secondary endpoints

The MCMC simulations for the primary endpoint will be used also for analysis of two secondary endpoints: PFS rate at 3 months and median PFS time.

- PFS rate at 3 months: For each pair of posterior values of γ and $\ln(\lambda)$ the PFS rate at 3 months is calculated using equation [2] with x=3. The calculated PFS rates at 3 months from the iterations form the posterior distribution for this secondary endpoint. The mean, median, standard deviation and 95% credible intervals for PFS rates at 3 months will be calculated from this posterior distribution.
- Median PFS time: For each pair of posterior values of γ and $\ln(\lambda)$ the median PFS time is calculated using equation [3]. The calculated median PFS times from the iterations form the posterior distribution for this secondary endpoint. The mean, median, standard deviation and 95% credible intervals for median PFS time will be calculated from this posterior distribution.

[redacted]

14.4 Appendix 4: Guidelines for response, duration of overall response, TTF, TT, progression-free survival and overall survival (based on RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

Document type:	TA Specific Guideline
Document status:	Version 3.1: 29-Nov-2011 Version 3:0: 19-Oct-2009 Version 2:0: 18-Jan-2007 Version 1:0: 13-Dec-2002
Release date:	29-Nov-2011

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

[redacted]

1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 2 and the definition of best response in Section 3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 4 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

2.1 Definitions

2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 3.2.8.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

[redacted]

- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 3.2.8.

2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

[redacted]

- 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 in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions

and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- Target lesions: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 2.1.1.
- **Nodal target**: See Section 2.1.1.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately

[redacted]

for the target (Table 14-6) and non-target lesions (Table 14-7) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-8) as well as the presence or absence of new lesions.

2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

2.4.1.1 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

2.4.1.2 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

[redacted]

2.4.2 Determination of target lesion response

Table 14-6 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.[2]
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
3. Methodology change See Section 2.2.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-6 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the

[redacted]

remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

[redacted]

2.4.3 Determination of non-target lesion response

Table 14-7 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

1. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm

[redacted]

there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion

- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 2.2.

2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-8.

Table 14-8 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. This overall lesion response also applies when there are no non-target lesions identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 2.4.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

[redacted]

3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- -For non-randomized trials where response is the primary endpoint, confirmation is needed.
- -For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response 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 where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).

[redacted]

- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

[redacted]

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

3.2 Time to event variables

The protocol should state which of the following variables is used in that study.

3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

[redacted]

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

3.2.4 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

3.2.5 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates… If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as

the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

3.2.6 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

[redacted]

3.2.7 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 3.2.8).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.

[redacted]

- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

3.2.8 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-9.

Table 14-9 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] As defined in Section 2.4.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

[redacted]

3.2.9 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-10 Options for event dates used in PFS, TTP, duration of response

Situation		**Options for end-date (progression or censoring)[1]** **(1) = default unless specified differently in the protocol or RAP**	**Outcome**
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1. =Definitions can be found in Section 3.2.7.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 3.2.7.
3. =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.

[redacted]

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-10 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

[redacted]

4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy

[redacted]

- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

4.4 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

4.5 Programming rules

The following should be used for programming of efficacy results:

4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and

[redacted]

assessment date is calculated as outlined in Section 3.2.7). 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 previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-10)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor

[redacted]

assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

5 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791.

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47.

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465.

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18.

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16.

[redacted]

14.5 Appendix 5: Management algorithms

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Novartis Medical Monitor. The guidance applies to all immuno-oncology (I-O) agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

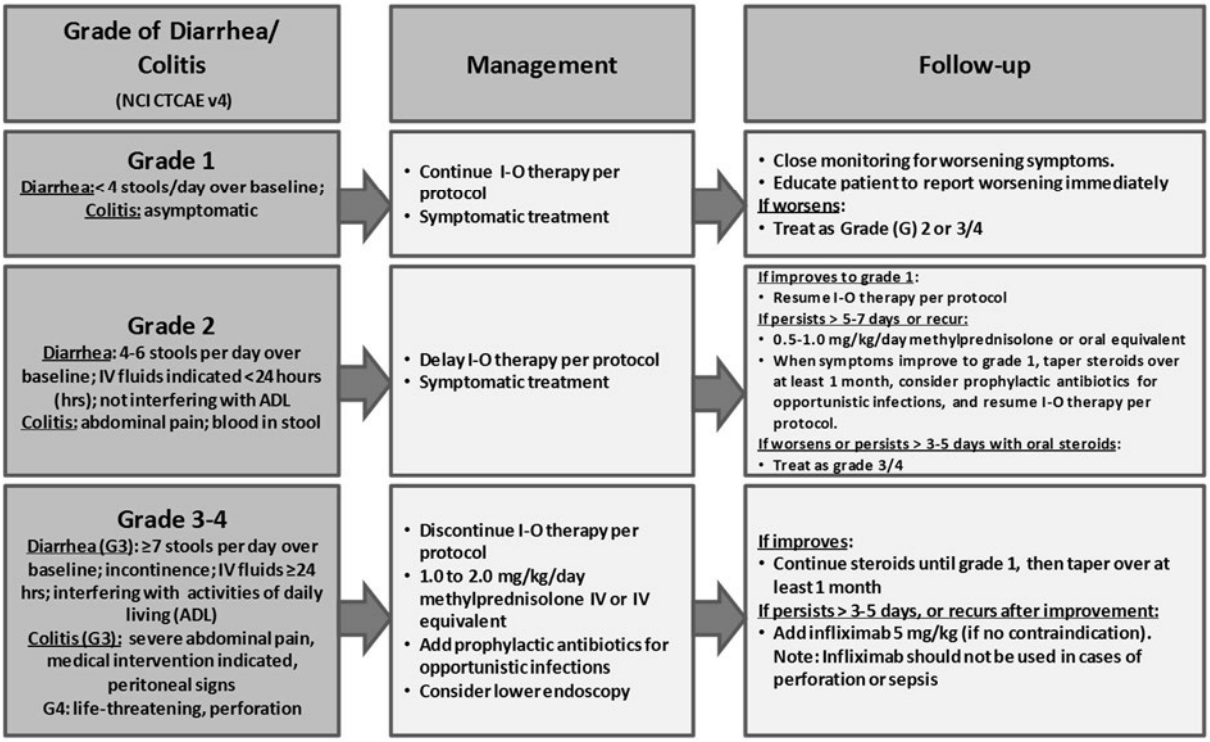
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

[redacted]

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

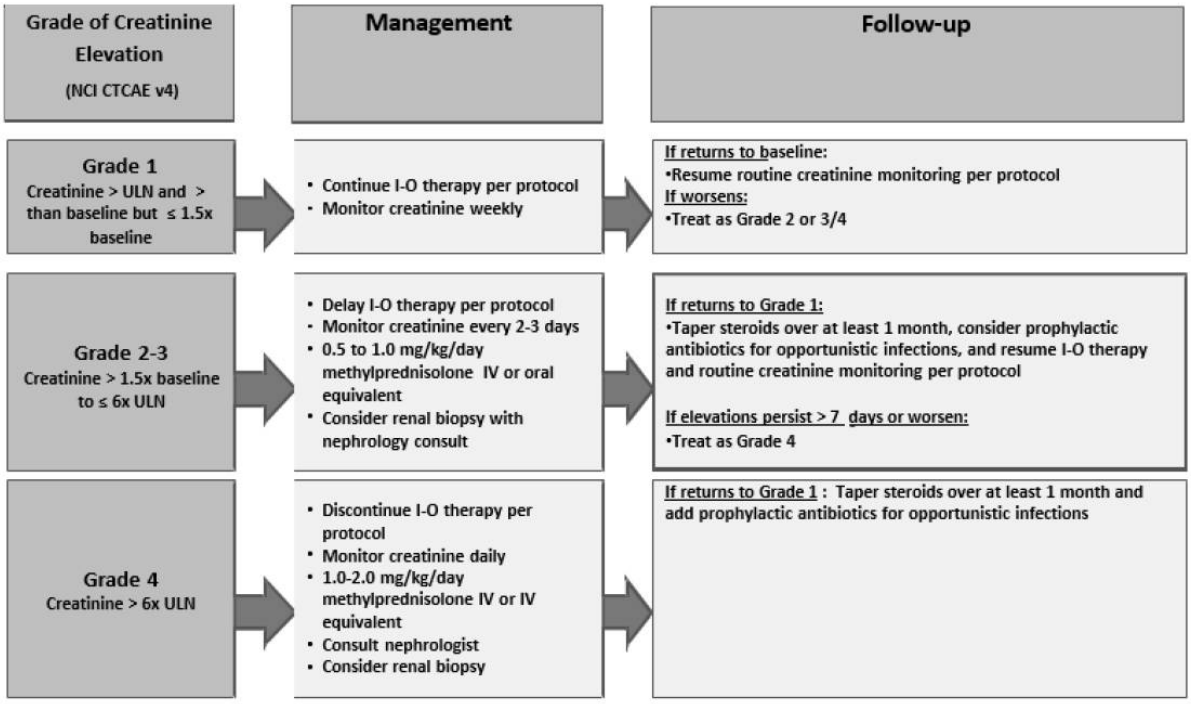


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

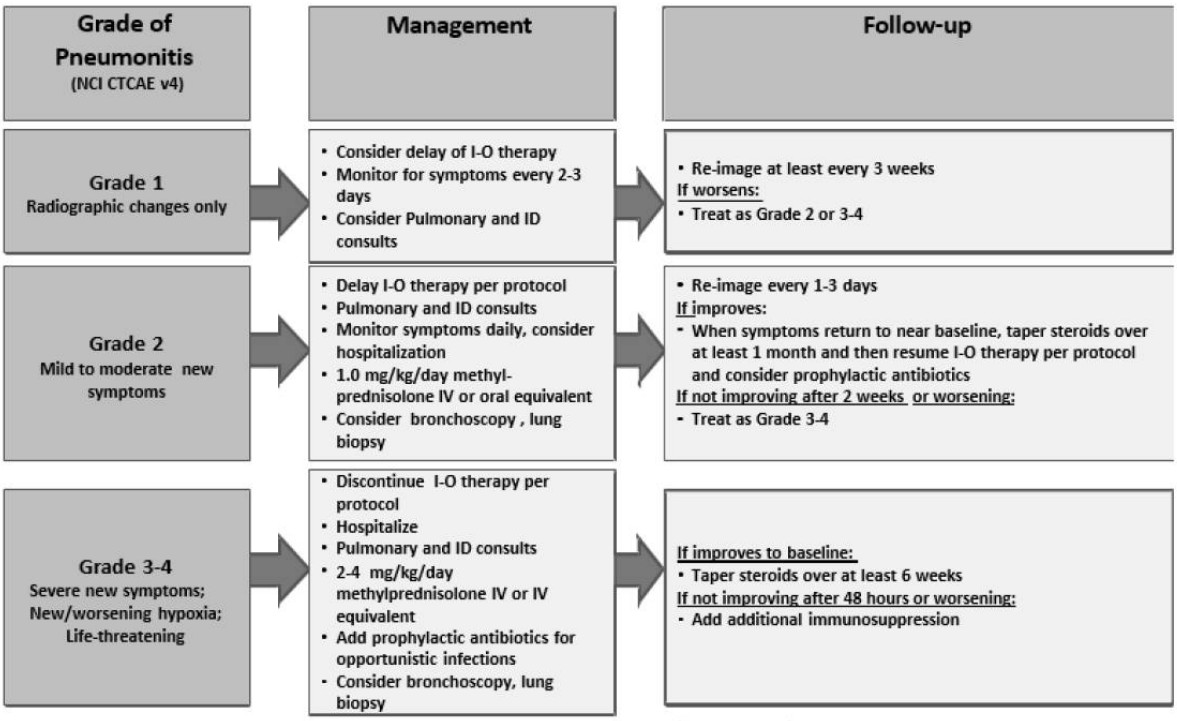


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

Pulmonary Adverse Event Management Algorithm

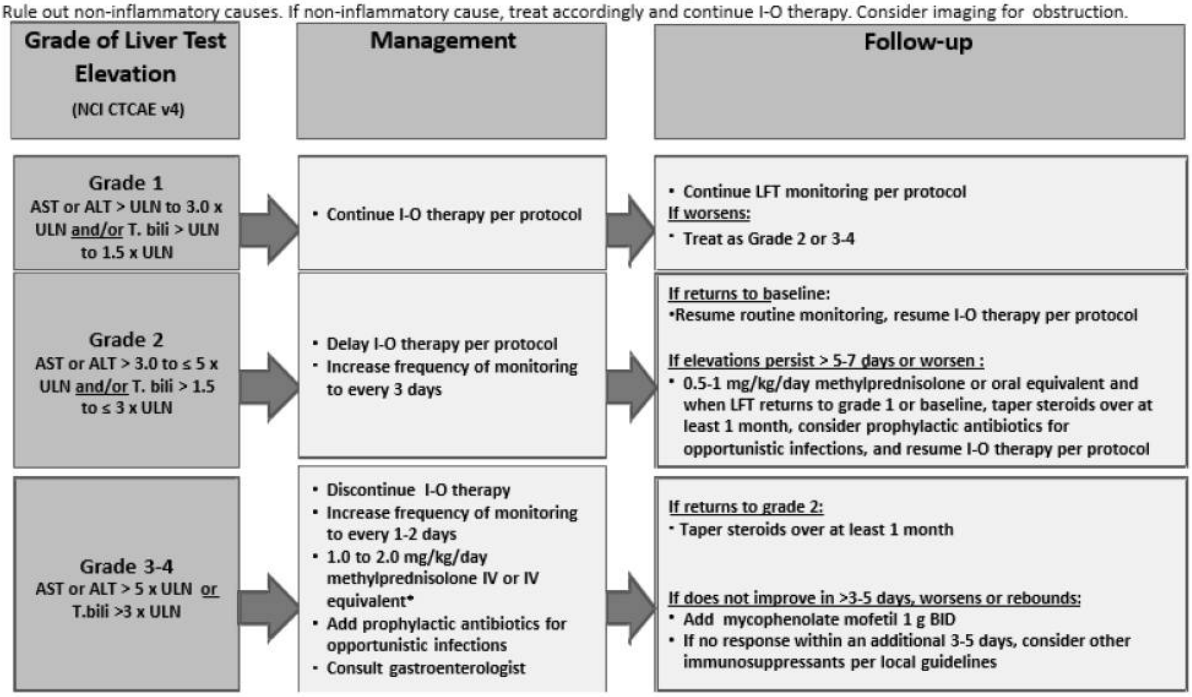
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



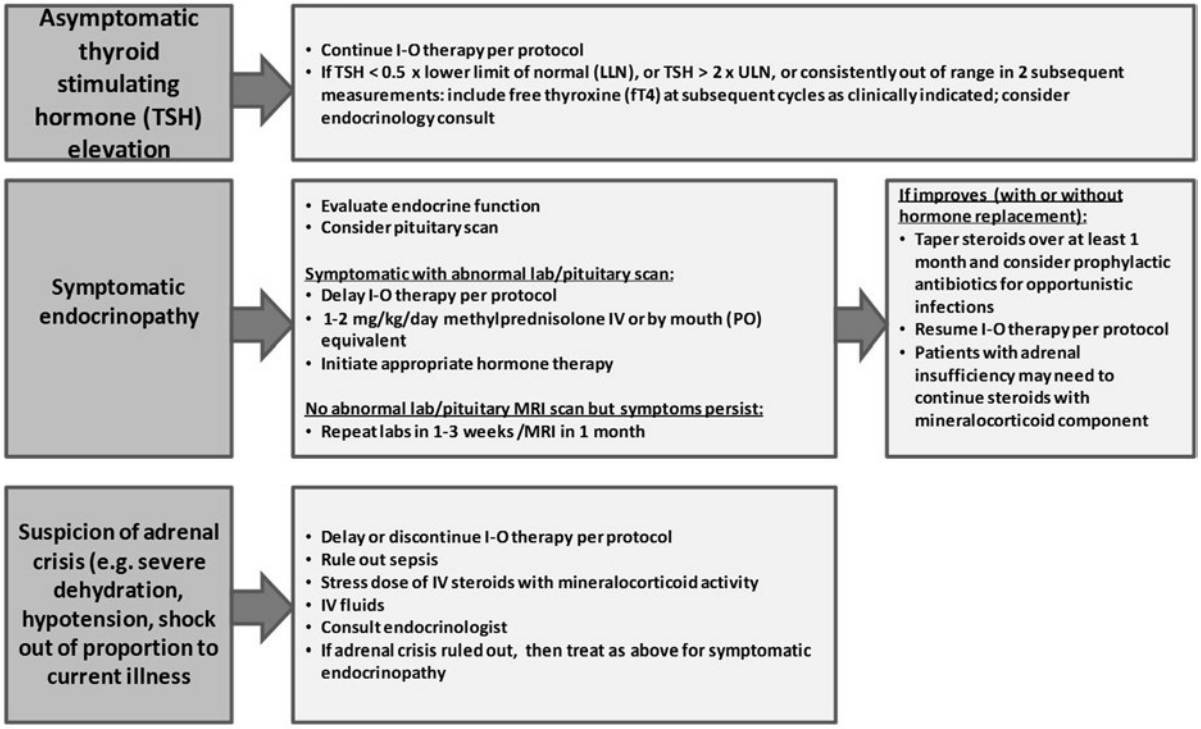
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

[redacted]

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

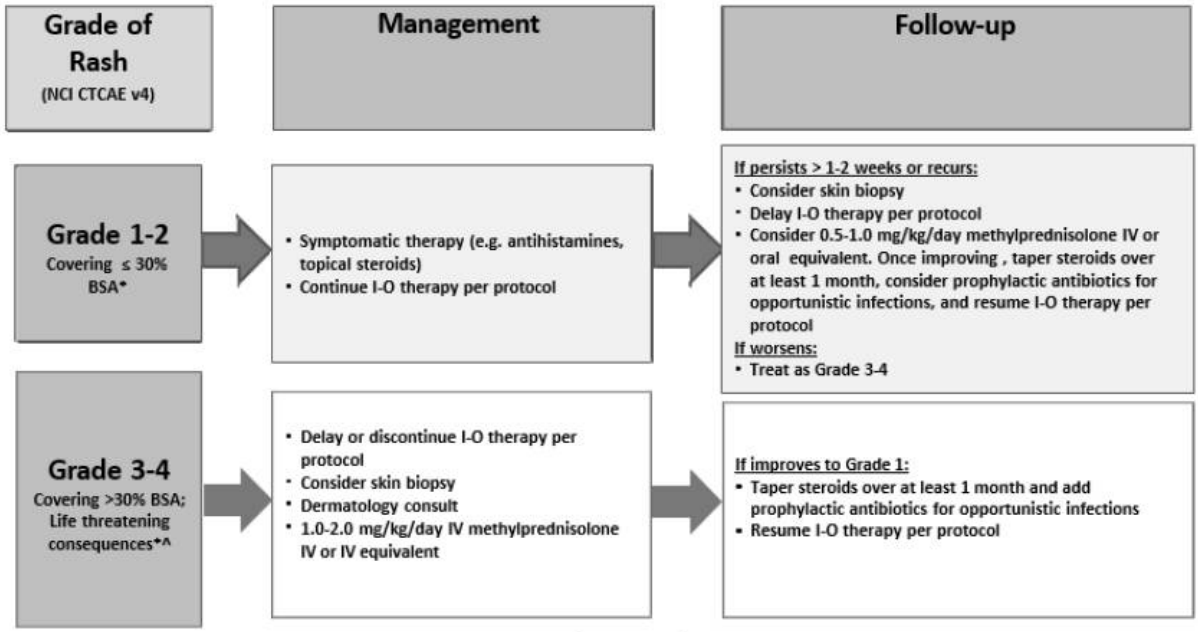


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

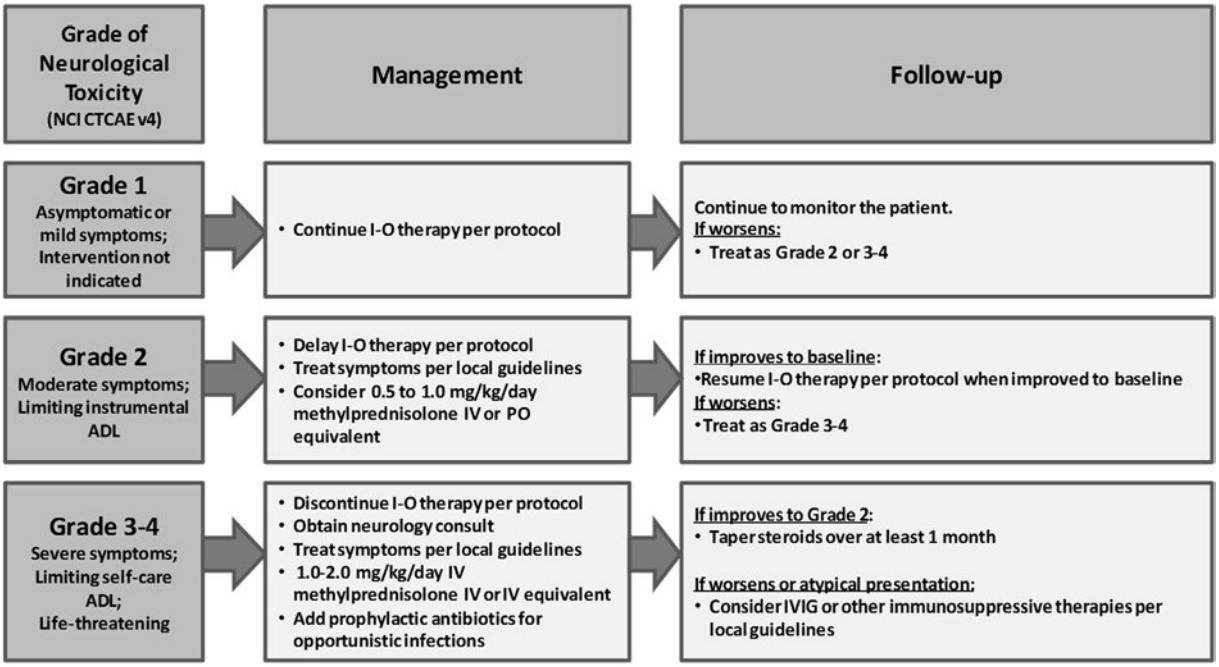
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

[redacted]

Neurological Adverse Event Management Algorithm

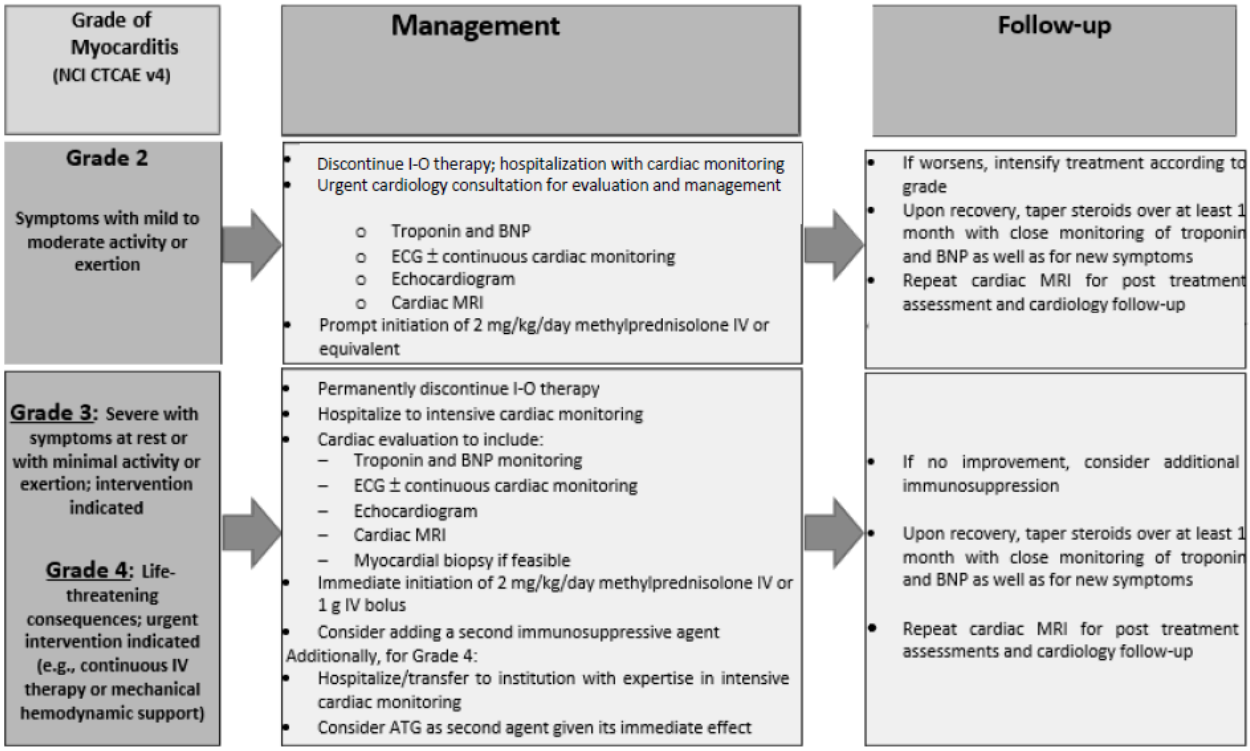
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

[redacted]

14.6 Appendix 6: Guidelines for viral hepatitis testing for ongoing and new patients

For all ongoing patients:

HBV testing

Screen all patients with HBV serologic markers: HBsAg, HBsAb, and HBcAb. If positive for either HBsAg and/or HBcAb, the patient should be discontinued/excluded from the study as required by the current protocol, and Novartis should be notified immediately. If positive only for HBsAb, HBV-DNA should be tested and if this returns positive the patient should be discontinued/excluded from the study as required by the current protocol, and Novartis should be notified immediately. Patients who are positive only for HBsAb and negative for HBV-DNA may continue on the protocol. Patients who screen negative for these serologic markers will continue on protocol.

HCV testing

Screen all patients with hepatitis C antibodies HC Ab and Hepatitis C RNA. If positive for either or both, the patient should be discontinued/excluded from the study as required by the current protocol, and Novartis should be notified immediately.

For all new patients:

HBV testing, treatment and monitoring

Screen all patients with HBV serologic markers: HBsAg, HBsAb, and HBcAb. If positive for either HBsAg and/or HBcAb, the patient should be excluded from the study as required by the current protocol, and Novartis should be notified immediately. If positive only for HBsAb, HBV-DNA should be tested and if this returns positive the patient should be excluded from the study as required by the current protocol, and Novartis should be notified immediately. Patients who are positive only for HBsAb and negative for HBV-DNA, and have a history of Hepatitis B vaccination, are eligible. Patients who screen negative for these serologic markers remain eligible.

HCV testing

Screen all patients with hepatitis C antibodies HC Ab and Hepatitis C RNA. If positive for either or both, the patient should be excluded from the study.

LFT monitoring and subsequent testing guidelines for all patients

LFTs should be monitored for all patients as per protocol, or more frequently if clinically indicated. At any time during the study, if ALT > 5 x ULN in patients with baseline ALT ≤ 3 x ULN, or if ALT > 8 x ULN in patients with baseline ALT > 3 x ULN but ≤ 5 x ULN: immediately

[redacted]

1. Perform test(s) for viral hepatitis infection or reactivation: all patients should be screened with viral hepatitis panel (HA Ab-IgM, HBsAg, HBcAb-IgM, HBV-DNA, HCV Ab, and HCV-RNA).
2. If any of the above tests indicate new viral infection or viral reactivation, immediately interrupt EGF816 treatment, consult a physician with expertise in managing viral hepatitis and contact Novartis for further discussion
3. Perform other relevant tests/procedures as clinically indicated
4. Follow the dosing modification for ALT elevation according to guidelines in the current protocol

[redacted]