NOVARTIS

Clinical Development

INC280, PDR001

Oncology Clinical Trial Protocol CINC280X2108 / NCT02795429

A phase Ib/II, open-label, multi-center study of INC280 in combination with PDR001 or PDR001 single agent in advanced hepatocellular carcinoma

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
ADL	Activities of Daily Life
AE	Adverse Event
AFP	Alpha Fetoprotein
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
APASL	Asia Pacific Association for the Study of Liver
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BCLC	Barcelona Clinic Liver Cancer
BID	Twice Daily
BLRM	Bayesian logistic regression model
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CMO&PS	Chief Medical Office & Patient Safety
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
eCRF	Electronic Case Report/Record Form
CRP	c-Reactive protein
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CSF	Colony Stimulating Growth Factor
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of Variation
DAR	Dose Administration Record
DBP	Diastolic Blood Pressure
DC	Dendritic Cells
DDI	Drug-Drug Interaction
DDS	Dose Determining Analysis Set
DILI	Drug-induced Liver Injury
DLT	Dose Limiting Toxicity
[redacted]	[redacted]
[redacted]	[redacted]
DOR	Duration of Overall Response
ECG	Electrocardiogram
EOT	End of Treatment
EWOC	Escalation with Overdose Control
FAS	Full Analysis Set
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FISH	Fluorescence In Situ Hybridization
FMI	Final market image

[redacted]

γ-IFN	Gamma-interferon
GCN	Gene copy number
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HBsAg	Surface Antigen to Hepatitis B
HBcAg	Core Antigen to Hepatitis B
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
hCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
HLA	Human Leucocyte Antigen
HR	Hazard Ratio
HNSCC	Head and Neck Squamous Cell Carcinoma
HNSTD	Highest Non-Severely Toxic Dose
IB	Investigator's Brochure
IC	Inhibitory Concentration
ICF	Informed Consent Form
IEC	Independent Ethics Committee
[redacted]	[redacted]
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial Lung Disease
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
irAE(s)	Immune-related Adverse Event(s)
irRC	Immune-related Response Criteria
IUD	Intrauterine Device
IUS	Intrauterine System
i.v.	Intravenous(ly)
LFT	Liver Function Test
LLOQ	Lower Limit Of Quantification
LMWH	Low Molecular Weight Heparin
mAb(s)	monoclonal Antibody(ies)
MAP	Meta-Analytic-Predictive
MF	Market Form
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NIRT	Novartis Interactive Response Technology
NKT Cells	Natural Killer T Cells
NSCLC	Non-Small Cell Lung Carcinoma
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PBMC	Peripheral Blood Mononuclear Cell

[redacted]

PD	Pharmacodynamics
PD-1	Programmed Death-1
PD-L1/2	Programmed Death-Ligand 1/2
PFS	Progression Free Survival
PK	Pharmacokinetics
p.o.	Per os
PPI	Proton-pump inhibitor
PT	Prothrombin Time
PPS	Per Protocol Set
cPR	Confirmed Partial Response
Q3W	Every 3 weeks
RAP	Report and Analysis Plan
RBC	Red blood cells
RCC	Renal Cell Cancer
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended phase 2 dose
RR	Response Rate
SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
SD	Stable Disease
SEC	Study Evaluation Completion
SHARP	Sorafenib HCC Assessment Randomized Protocol
SJS	Stevens-Johnson Syndrome
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEN	Toxic Epidermal Necrolysis
TIL(s)	Tumor Infiltrating Lymphocyte(s)
TdP	Torsades de Pointes
TKI	Tyrosine Kinase Inhibitor
Treg	Regulatory T Cell
TTP	Time To Progression
TTR	Time To Response
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cells
WOC	Withdrawal of study consent

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
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.: q21 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
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)
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
Subject/Patient Number (Patient No.)	A unique identifying number assigned to each subject/patient 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
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 a patient permanently discontinues taking 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 study consent (WOC)	Withdrawal of consent 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]

Amendment 5 (14-Feb-2020)

Amendment rationale

The primary purpose of this amendment is to incorporate dose modification and management guidelines for myocarditis, as well as the option for patients to be transferred to another study or an alternative treatment option to continue study treatment at the time of end of this study.

After a recent occurrence of a case of myocarditis, the dose modification guidelines for protocols using INC280 in combination with PDR001 were updated to mandate permanent discontinuation of study treatment in case of myocarditis grade ≥2 or other cardiac event grade ≥3. In addition, recommended clinical management guidelines in case of such an event have been provided.

This protocol amendment revises the definition of end of study to include the option for patients still on study treatment and who, in the opinion of the investigator, are still deriving clinical benefit at the time of end of study, to transfer to another study or to an alternative treatment option to continue providing study treatment to these patients.

Furthermore, the withdrawal of consent language was revised to differentiate sample use after a patient withdraws consent based on the different regulations/laws around the world.

Study status

This study started enrollment on 15-Jun-2016. As of 06-Feb-2020, a total of 27 patients have been treated with INC280 in combination with PDR001 in the dose escalation part of the study. In the Phase II part of the study, 32 patients have been treated with INC280 in combination with PDR001 and 30 patients with PDR001 single agent. Enrollment was closed on 27-Aug-2019.

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.

- Glossary of terms: Addition of personal data and update of withdrawal of study consent definition.
- Section 4.3, Definition of end of study has been revised including the option for patients to continue study treatment within another study or to an alternative treatment option.
- Table 6-5, Dose reduction and interruption criteria: Updated to reflect the permanent discontinuation of study treatment in case of myocarditis grade ≥ 2 or other cardiac event grade ≥ 3, and inclusion of recommended clinical management guidelines.
- Table 7-1, Visit schedule and assessments: It has been clarified that concomitant medication only has to be collected until the 30-day safety follow-up or the start of new antineoplastic therapy.
- Section 7.1.3, Discontinuation of study treatment: Addition of language to specify that patients who transfer to another study or an alternative treatment option to continue provision of study treatment will complete end of treatment procedures.

[redacted]

- Section 7.1.4, Withdrawal of consent: This section has been updated to match the latest protocol template language.
- Section 7.1.5, Follow-up period: Addition of language to specify that patients who transfer to another clinical study or an alternative treatment option to continue provision of study treatment will not complete the safety, disease progression, and survival follow-up.
- Section 8.3, Pregnancies: Based on the revised pregnancy guidance, the follow-up duration for a newborn has been changed from 3 months to 12 months.

Additional clarifications were made for consistency reasons and to correct minor editing changes from previous version.

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. In addition, if 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 amended protocol.

[redacted]

Amendment 4 (14-Sep-2018)

Amendment rationale

The primary purpose of this amendment is to incorporate health authority-requested language requiring study treatment discontinuation in the event of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).

After the recent occurrence of a case of Stevens-Johnson syndrome in a study with PDR001 in combination with another investigational agent, the dose modification guidelines for protocols using PDR001 were updated to mandate permanent discontinuation of study treatment for patients who experience SJS or Lyell syndrome/toxic epidermal necrolysis (TEN). This change has already been implemented as part of an urgent safety measure released on 15-Jun-2018. This protocol amendment is now formalizing these changes in the dose modification section and corresponding table describing the criteria for dose reduction/interruption and re-initiation of treatment for adverse drug reactions (Table 6-5, Dose reduction and interruption criteria).

In addition, based on a health authority request, patients with indolent malignancies that have never required therapy will no longer be considered eligible for this study. Exclusion criterion #23 'Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type' has been updated accordingly.

Study status

This study started enrollment on 15-Jun-2016. As of 10-Sep-2018, a total of 27 patients had been treated with INC280 in combination with PDR001 in the dose escalation part of the study, and in the Phase II part of the study 8 patients with INC280 in combination with PDR001 and 8 patients with PDR001 single agent.

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.

- Section 5.3, Exclusion criterion #23: Removal of 'Any malignancy considered to be indolent and that has never required therapy'.
- Table 6-5, Dose reduction and interruption criteria: Updated to reflect the permanent discontinuation of study treatment in case of SJS or TEN, as per the USM letter of 15-Jun-2018.

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 in this amendment identified above as being related to the USM have already been implemented by a USM letter issued on 15-Jun-2018. These changes are required for patient

[redacted]

safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore, they were required to have been implemented prior to IRB/IEC approval of this amendment.

The other change described in this amended protocol requires 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 3 (27-Mar-2018)

Amendment rationale

The main purpose of this amendment is to update the exclusion criteria, the list of prohibited medications, the list of medications to be used with caution and the criteria for dose modifications based on the latest INC280 clinical data as per INC280 Investigator‘s Brochure edition 8 with primary focus on pneumonitis/ILD events that have been reported with INC280.

Pneumonitis and ILD have been reported from both INC280 single agent and combination studies with the EGFR TKIs, including events with fatal outcome. Dose modification guidelines for INC280 have been implemented in this protocol amendment for patients with pulmonary symptoms indicative of ILD/pneumonitis.

Additional PK analysis has been performed to evaluate the effect of food and concomitant medications on INC280 exposures. There data are summarized in Section 1.2.1, entitled Overview of INC280. Based on the food effect evaluations, INC280 may be taken with or without food in this study. In addition, based on preliminary analysis from the DDI studies, in which strong CYP3A4 inhibitors did not significantly impact INC280 exposure and INC280 was evaluated only as a moderate CYP1A2 inhibitor. CYP3A4 inhibitors and CYP1A2 substrates with NTI have been removed from prohibited concomitant therapy and added to permitted concomitant medications to be used with caution. Furthermore, the protocol includes some updates on other prohibited concomitant medications and the permitted concomitant medications to be used with caution based on preliminary DDI study results.

Monoclonal antibodies are not genotoxic due to their high molecular weight, and are not expected to interact with DNA. In addition, they have a low distribution to the semen, a relatively small volume of semen delivered to the partner, and very low absorption. Fetal harm from semen delivery is therefore biologically implausible and the amount of monoclonal antibodies able to gain access to the partner’s systemic circulation via trans-epidermal transfer would be expected to be extremely low. Therefore, the use of condom for male study participants receiving PDR001 is no longer required.

Additional clarifications were made for consistency reasons and to correct minor editing changes from previous version.

Study status

This study started enrollment on 15-Jun-2016. As of 27-Mar-2018, a total of 27 patients had been treated with INC280 in combination with PDR001 in the dose escalation part of the study.

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.

- Protocol summary has been updated according to the changes made in main text of the protocol.
- Section 1.2.1.2, INC280 clinical experience has been updated to match the current INC280 Investigator’s Brochure.

[redacted]

- Section 1.2.3.1, Non-clinical and clinical experience with the combination of INC280 and PDR001 was updated to reflect the current status of this study.
- Section 5.3, Exclusion criteria:
  - Exclusion criterion #1 has been updated to be in line with inclusion criterion #9.
  - Exclusion criterion #6 has been added to exclude patients with presence or history of interstitial lung disease or interstitial pneumonitis.
  - Exclusion criterion #18 has been updated to allow strong CYP3A4 inhibitors and CYP1A2 substrates with narrow therapeutic index.
  - Exclusion criterion #26 has been updated to no longer mandate use of condoms during intercourse during PDR001 treatment and after the last dose of PDR001.
- Section 6.1.1, Dosing regimen: It has been specified that INC280 can be administered with or without food.
- Table 6-5, Dose reduction and interruption criteria: Recommended dose modifications for ILD like events/pneumonitis have been added.
- Section 6.3.3.2, Follow-up on potential drug-induced liver injury (DILI) cases: It has been specified that potential drug-induced liver injury has to be reported as SAE.
- Section 6.5.2, Permitted concomitant therapy requiring caution and/or action has been updated to be in line with Appendix 6.
- Section 6.5.3, Prohibited concomitant therapy has been updated to be in line with Appendix 5 and corticosteroid wording has been re-formatted for better readability.
- Section 7.1.5, Follow-up period: Timepoints for disease progression follow-up have been updated to be consistent with Table 7-1.
- Table 14-17, Drugs prohibited while on study: Strong and moderate CYP3A4 inhibitors as well as substrates of CYP1A2 with narrow therapeutic index have been removed.
- Table 14-18, Drugs with a known risk of torsades de pointes has been updated with categories removed and drugs sorted alphabetically.
- Table 14-19, Drugs to be used with caution while on study has been updated to include strong CYP3A inhibitors and CYP1A2 substrates with NTI. H2 receptor antagonists, PPI and antacids have also been added and the list of P-gp and BCRP substrates has been updated and sorted alphabetically. Moderate CYP3A4 inducers, sensitive substrates of CYP3A4, CYP2C8, CYP2C9 and CYP2C19, and substrates of OATP 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. In addition, if 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 amended protocol.

Amendment 2 (07-Nov-2017)

Amendment rationale

The main purpose for this amendment is threefold. The first is to reduce the focus on the cMET high population; the second is to expand the eligible clinical population to include patients with Hepatitis C virus (HCV), and patients with mild ascites; and the third to introduce additional biomarker collections based on emerging pharmacodynamic data.

The prospective patient stratification by cMET status in the Phase II will be removed, based on new pre-clinical data. Recent preclinical studies show that inhibition of MET by pharmacological or genetic means can enhance T cell mediated anti-tumor immunity in a variety of treatment regimens and mouse models (Glodde et al 2017). Consistent with these reports, internal data from Novartis in two syngeneic mouse models demonstrate that the combination treatment of PDR001 with INC280 led to increased T cell infiltration and an improved anti-tumor immune response with a higher cure rate than single agent PDR001. Importantly, neither of the cell models are sensitive to single-agent INC280 in vitro and neither have high cMET expression, suggesting the added benefit of INC280 to PDR001 is not dependent on autonomous cMET signals and further supporting the clinical evaluation of the combination in a molecular unselected patient population.

Based on these observations, with this amendment, patients will no longer be prospectively stratified by cMET status and will be enrolled without molecular pre-selection. Testing for cMET will be done retrospectively. The primary objective of this study has been updated to "to compare the efficacy of INC280 in combination with PDR001 vs. PDR001 single agent" in all patients, and not by c-MET molecular status. The secondary objectives that were specific to each molecular population have also been adjusted or removed.

The patient population in this study will be expanded to include patients with detectable HCV. This is based on the emerging data showing that patients with HCV associated HCC can derive benefit from checkpoint inhibitors without apparent addition of treatment related risks. Patients with HCV were enrolled and treated on study [CINC280X2201], and no additional toxicities were observed in this population. In addition, patients with clinically insignificant ascites will be permitted on this study. This change is in line with other clinical studies in HCC, and recognizes that imaging performed with the intent of tumor evaluation can detect ascites, which may not be otherwise clinically significant.

[redacted] This is based on current data that indicate that response to drugs targeting checkpoint inhibitors may depend on the mutation burden of the tumor (Rizvi et al 2015). [redacted] Another sample from these patients will be collected at the end of the trial (EOT) if the reason for discontinuation is progression of disease. Furthermore, an optional tumor sample is requested at progression of disease only for patients who had a response as per investigator assessment. [redacted]

[redacted]

[redacted]

In addition, clinical assessments of Child Pugh status will be introduced every 3 cycles in order to better assess the underlying disease/prognosis throughout the study.

To reduce patient burden, serology tests (Anti-DNA antibodies (Abs), Anti-nuclear abs, Anti-phospholipid abs, Anti-mitochondrial abs, c-Reactive protein (CRP), Rheumatoid factor (RF)) are no longer mandated.

Also based on results from a recent clinical study, [CINC280A2103], a drug-drug interaction (DDI) study with Midazolam (a CYP3A4 substrate), the restriction on co-administration with CYP3A4/5 substrates with narrow therapeutic indexes will be removed.

Additional clarifications were made for consistency reasons.

Study status

The CINC280X2108 study started enrollment on 15-Jun-2016. As of 18-Oct-2017, a total of 21 patients had been treated with INC280 in combination with PDR001 in the dose escalation part of the study.

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.

- Protocol summary has been updated according to the changed made in main text of the protocol.
- Section 2.2, Rationale for study design, phase II:
  - Removal of stratification by cMET status.
- Table 3-1, Objectives and related endpoints:
  - Update of primary and secondary objectives to match the new study design.

[redacted]

- Figure 4-2, Study flow: Removal of pre-screening.
- Section 5.2, Inclusion criteria:

[redacted]

  - Inclusion criterion #3 has been updated with the addition of Asian Pacific Association for the Study of the Liver (APASL) as well as allowing patients with controlled ascites.
  - Inclusion criterion #5 mandating documented evidence of cMET status for Phase II has been removed.
  - Inclusion criterion #13 excluding HCV has been removed.
- Section 5.3, Exclusion criteria:
  - Exclusion criterion #2: Updated with only live vaccines to be prohibited.
  - Exclusion criterion #17 has been updated excluding strong inducers or inhibitors of CYP3A4/5 and allowing CYP3A substrates with narrow therapeutic index.
  - Exclusion criterion #20: Thresholds for PT and INR have been corrected.
- Table 6-1, Starting dose and treatment schedule and section 6.7.1, Study drug packaging and labeling: 'Lyophilisate in vial' has been replaced by 'powder for solution for infusion'.
- Section 6.1, Study treatment, PDR001 and section 6.3.1, Dose modification and dose delay for PDR001: Instructions for PDR001 dose delay have been updated.
- Section 6.3.1, Dose modifications and dose delay for INC280 has been added.
- Section 6.4, Anticipated risks and safety concerns of the study drug (PDR001 and INC280) has been updated according to the latest protocol template.
- Table 6-5, Dose reduction and interruption criteria: Addition of criteria in case of peripheral edema.
- Section 6.5.1, Permitted concomitant therapy: The timeframe for recording concomitant medication has been specified.
- Section 6.5.3, Prohibited concomitant therapy: For the use of immunosuppressive drugs, the exception of prophylaxis against imaging contrast dye allergy has been added, corticosteroid treatment has been further specified, use of vaccines and drugs with a known risk of causing TdP have been clarified.
- Section 6.6.1, Patient numbering: Pre-screening has been deleted.
- Section 6.6.2, Randomization Phase II part: NIRT registration process has been clarified.
- Section 7.1.1, Molecular pre-screening has been deleted.
- Section 7.1.5, Follow-up period:
  - Clarification regarding safety follow-up visit has been added.
  - Time window of +/-7 days for survival follow-up contact has been specified.
  - Time point to switch frequency of response evaluation has been updated for practicality reasons.
- Section 7.1, Study flow and visit schedule:
  - Removal of molecular screening.
  - Follow-up period: Addition of time window +/-7 days for survival follow-up contact.
  - Time point to switch frequency of response evaluation has been updated for practicality reasons.

[redacted]

  - Addition of Child Pugh status.
  - Time point for Alpha Fetoprotein has been moved from pre-screening to screening.
  - [redacted]
  - Removal of serology exam.
- Table 7-2, Disease assessment plan:
  - Time point to switch frequency of response evaluation to every three cycles has been updated for practicality reasons.
  - It has been clarified that screening brain MRI is only mandated in case of suspected brain metastases.
- Section 7.2.2, Safety and tolerability assessments: Child Pugh status has been added.
- Table 7-4, Local/Central clinical laboratory parameters clinical collection plan: Removal of serology exam in serum.
- Table 7-9, Schedule of blood collection for PDR001 PK and IG (serum) for patients participating in phase II: The time window for 1h post dose time point has been extended to 15 minutes, due to practicality reasons.
- Table 7-10, Biomarker sample collection plan:
  - Addition of time point for optional biopsy at progression of disease for patients who had a response.
  - [redacted]
- Section 7.2.4.1.2, Pharmacodynamic assessments in tumor samples: Addition of tumor biopsy at progression; removal of Nanostring.
- [redacted]
- Section 8.1, Adverse Events, definitions and reporting: Section regarding molecular ICF has been deleted and wording has been added to specify AE collection after initiation of new antineoplastic treatment.
- Section 8.2, Serious Adverse Events, reporting: Section regarding molecular ICF has been deleted and wording has been added to specify AE collection after initiation of new antineoplastic treatment.
- Section 10, Statistical methods and analysis:
  - Update of study arms to reflect the change in study design.
- Section 10.4, Primary objective Phase II part: Modification of primary objectives to reflect the change in study design.
- Section 10.4.2.2, Phase II part: Patient classification in cMET high/low group has been removed.

[redacted]

- Sections 10.5.2.2, Association of cMET status with PDR001 single agent anti-tumor effect and 10.5.2.3, Comparison of efficacy of INC280+PDR001 vs. INC280 single agent in cMET high patients, have been removed.
- Section 10.4.3.1, Analysis set and grouping for the analyses: Observation period has been re-defined.

[redacted]

- Section 10.8, Sample size calculation, Phase II part, has been updated to reflect the change in study design.
- Section 11.5, Publication of study protocol and results has been updated to match the most recent protocol template.
- Appendix 3, Statistical considerations has been updated to reflect the change in study design.
- Appendix 5, Prohibited concomitant medication: Appendix has been replaced by the current updated version.
- Appendix 6, Concomitant medication to be used with caution: Appendix has been replaced by the current updated version.

Other minor/editing changes in the protocol text were made for clarification.

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. In addition, if 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 amended protocol.

[redacted]

Amendment 1 (27-Jun-2016)

Amendment rationale

Based on Health Authority requests, the following changes have been implemented in this protocol:

- Patients who refused sorafenib treatment have been excluded from the patient population to be enrolled in this study. To be eligible, patients must have received prior systemic sorafenib treatment for HCC with documented progression during or after discontinuation of sorafenib treatment, or are intolerant to sorafenib (that led to sorafenib discontinuation).
- A mandatory HIV test has been introduced at screening. Considering the limited clinical experience with PD-1 inhibitors in HIV positive patients, to reduce the potential risk of virus reactivation, HIV testing has been mandated and HIV positive patients will be excluded from the study.
- Thrombocytopenia CTCAE grade 3 with clinically significant bleeding has been listed as DLT, as well as nausea/vomiting grade 4 (regardless of anti-emetic treatment) and diarrhea grade 4 (regardless of anti-diarrheal treatment).
- Enrollment of patients potentially eligible for any loco regional liver treatment (e.g. hepatic resection, hepatic arterial embolization, radiofrequency ablation) is not allowed.
- History of organ transplant has been added as an additional exclusion criterion. Limited data are reported for the efficacy and toxicity, such as organ rejection, of immune checkpoints including PD-1 inhibitors in patients with organ transplant, therefore considering the risk, patients with a history of organ transplant will be excluded from the study.

The following further changes have been implemented in this protocol:

Corticosteroids and immunosuppressive therapy are widely used agents in the treatment of numerous autoimmune and inflammatory diseases and they may interfere with the therapeutic efficacy of the immune checkpoints including PDR001, therefore an exclusion criteria about their systemic use has been included.

With the available PK data obtained from the single agent first-in-human study [CPDR001X2101], an exploratory population PK (PopPK) analysis showed that the T1/2 of PDR001 in man is 20 [17, 23] days (mean [90% CI]). Using five times the upper limit of the half-life of 23 days and an added safety margin, the protocol is amended to increase the duration of contraception and safety follow-up periods post PDR001 treatment from 90 days to 150 days. These changes are related to an Urgent Safety Measure communicated on 08-June-2016 to all investigators.

Section 1.2.1.3, Clinical pharmacology has been updated to add a rationale why the concomitant use of acid reducing agents, including PPI, gastric acid modulators and H2 receptor antagonists, is unlikely to have impact on the efficacy of INC280.

[redacted]

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.

- Protocol summary: Secondary objectives have been updated to be aligned with Table 3-1.
- Section 1.2.1.3: A paragraph summarizing the results of PPI study has been added.
- Section 2.1, Section 2.2 and Section 5.2, Inclusion criterion #7: Patients who refused sorafenib treatment have been excluded from the patient population.
- Section 4.1, Study flow, Section 5.3, Inclusion criteria 25 and 26, Section 6.3.2, Follow-up toxicities related to PDR001, Section 7.1, Study flow and visit schedule, Section 7.1.6, Follow-up period, Section 8.1.1, Definitions and Reporting, Section 8.2.2, Reporting, and
- Section 10.5.3, Safety objectives: Safety follow-up period for PDR001 has been extended to 150 days.
- Figure 4-2 has been updated: Pre-screening and 30 days/150 days safety follow-up added.
- Section 5.2: Inclusion criterion #3: It has been specified that diagnosis can either be done histologically or cytologically, or for subjects with cirrhosis clinical diagnosis of HCC according to the American Association for the Study of Liver Diseases (AASLD) criteria.
- Section 5.3, Exclusion criterion #4 has been added.
- Section 5.3, Exclusion criterion #9 has been added to specify corticosteroids use.
- Section 5.3, Exclusion criterion #10 has been added: Interferon use within 2 weeks of the first dose of study treatment.
- Section 5.3, Exclusion criterion #13 has been amended with mandatory HIV testing at screening.
- Section 5.3, Exclusion criterion # 14 has been added to exclude patients with a history of organ transplant.
- Section 5.3, Exclusion criteria #25 and #26: Contraception period for PDR001 has been extended to 150 days.
- Table 6-3: Thrombocytopenia CTCAE grade 3 with clinically significant bleeding has been added to the DLT table.
- Table 6-3: Nausea/Vomiting CTCAE grade 4 and diarrhea grade 4 have been added to the DLT table.
- Section 7.1, Study flow and visit schedule: It has been specified, that the time window for tumor biopsies in the Phase Ib may be longer than 21 days.
- Table 7-1 and Table 7-4: HIV testing has been added.
- [redacted]
- Table 7-1 and section 7.2.2.5.7: Alpha Fetoprotein (AFP) has been added to have consistency between section 10.6.2 and Table 7-1 (for phase II only).
- Table 7-2: To be consistent with section 7.2.1, Screening assessments, it has been specified that brain CT/MRI at baseline should only be done in case of known brain metastases or symptoms.
- Table 7-4: It has been specified that cytokines and serology will be assessed centrally.

[redacted]

- Section 7.2.2.5.9, Pregnancy assessments: Additional time points for urine pregnancy test have been added.
- Section 10.1.4: Minimum exposure criterion has been updated.
- Appendix 7: Child-Pugh classification has been added.

Other minor/editing changes in the protocol text were made for clarification.

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. In addition, if 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 amended protocol.

[redacted]

Protocol Summary:

Protocol number	CINC280X2108
Title	A phase Ib/II, open-label, multi-center study of INC280 in combination with PDR001 or PDR001 single agent in advanced hepatocellular carcinoma
Brief title	Phase Ib/II study of INC280 + PDR001 or PDR001 single agent in advanced HCC
Sponsor and Clinical Phase	Novartis Phase Ib/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study of INC280 and PDR001 is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of PDR001 administered i.v. as a single agent or in combination with INC280 administered orally in adult patients with advanced hepatocellular carcinoma (HCC).
Primary Objective(s)	Phase Ib: To characterize the safety and tolerability of INC280 in combination with PDR001 and to identify the Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D). Phase II: To compare the efficacy of INC280 in combination with PDR001 vs. PDR001 single agent.
Secondary Objectives	• To characterize the safety and tolerability of INC280 combined with PDR001 and PDR001 single agent in the phase II part • To further characterize the efficacy of INC280 in combination with PDR001 and PDR001 single agent • To characterize the pharmacokinetic profile of INC280 combined with PDR001 and PDR001 single agent • To assess the pharmacodynamic effect of INC280 in combination with PDR001 and PDR001 single agent in tumor biopsy
Study Design	This is a phase Ib/II, open-label, multi-center study which consists of a phase Ib dose escalation part of INC280 in combination with PDR001 in advanced HCC. Once the Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D) of INC280 in combination with PDR001 is achieved, a phase II part in patients with advanced HCC with INC280 in combination with PDR001 and PDR001 single agent will commence. INC280 will be administered orally BID on a continuous schedule, and PDR001 will be administered i.v. every three weeks until a patient experiences unacceptable toxicity, progressive disease (PD) as per irRC and/or treatment is discontinued at the discretion of the Investigator or the patient. Patients should not discontinue treatment based on progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 unless clinical deterioration or increase in tumor markers is observed.
Population	This study will be conducted in adult patients with advanced HCC.
Inclusion criteria (selected)	1. Histologically or cytologically documented locally advanced recurrent or metastatic HCC or for subjects with cirrhosis clinical diagnosis of HCC according to the American Association for the Study of Liver Diseases (AASLD) (2011) and Asian Pacific Association for the Study of the Liver (APASL) (2010) criteria. Current cirrhotic status of Child Pugh Class A (5-6 points), with no encephalopathy and/or clinically significant ascites (defined as requiring diuretic or paracentesis treatment). Child Pugh status must be calculated based on clinical and laboratory results during the screening period. 2. Baseline tumor tissue (newly obtained) must be available at screening. Patient must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution's guidelines and requirements for such procedure. 3. Patients must be willing to undergo a new tumor biopsy during the study (6-9 weeks after start of study treatment, if medically feasible). For patients in the phase II part of the study, exceptions may be granted after documented

[redacted]

	discussion with Novartis. After a sufficient number of paired biopsies are collected, the decision may be taken to stop collecting the biopsies. 4. Patients must have received prior systemic sorafenib treatment for HCC with documented progression during or after discontinuation of sorafenib treatment (for France only: patients must have received at least 8 weeks of prior sorafenib treatment), or are intolerant to sorafenib (defined as documented Grade 3 or 4 adverse events that led to sorafenib discontinuation). 5. Patients must be tested during screening for Hepatitis-B-Virus surface antigen (HbsAg) status. Patients are included in the study if they have adequately controlled hepatitis B, defined by: • receiving a nucleoside analog anti-viral drug for 3 or more months, and • serum hepatitis B virus (HBV) deoxyribonucleic acid (DNA) level of less than 100 IU/ml via polymerase chain reaction quantification assays prior to enrollment.
Exclusion criteria (selected)	1. Patient has received the following therapies prior to the first dose of study treatment: • Previous systemic anti-cancer therapy (including therapeutic cancer vaccines and immunotherapeutics) other than sorafenib (sorafenib must be completed within > 2 weeks prior to the first dose of study treatment) or INC280. • Previous locoregional therapy (e.g. hepatic arterial embolization, radio-frequency ablation, radiation therapy) if: • administered after sorafenib treatment with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain. Loco regional therapy for the focally painful liver tumor mass will be discussed on a case by case with Novartis. • completed within 4 weeks prior to the dosing and, if present any related acute toxicity grade > 1. 2. Use of any live vaccines within 4 weeks of initiation of study treatment. 3. Major surgery within 2 weeks of the first dose of study treatment (mediastinoscopy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery). 4. Participation in an interventional, investigational study within 2 weeks of the first dose of study treatment, unless agreed otherwise with Novartis. 5. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention). 6. Presence of CTCAE grade ≥1 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if CTCAE grade ≥ 3) due to prior cancer therapy, unless agreed otherwise with Novartis. 7. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) ≤ 2 weeks prior start or study drug. An erythroid stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the patient is on a stable dose. 8. History of severe hypersensitivity reactions to other monoclonal antibodies (mAbs). 9. Positive human immunodeficiency virus (HIV) test at screening or known history of testing positive for HIV or known acquired immunodeficiency syndrome. 10. Clinically significant pleural effusion that either required pleurocentesis or is associated with shortness of breath. 11. Patients receiving treatment with medications that are strong inducers of CYP3A4 and that cannot be discontinued at least 1 week prior to the start of treatment with INC280 and for the duration of the study.

[redacted]

	12. Unable to stop herbal/food supplements or treatments which are considered to be capable of significantly causing either PK or PD herb/food-drug interactions. 13. Active autoimmune disease or a documented history of autoimmune disease, including ulcerative colitis and Crohn's disease or any condition that requires systemic steroids or any immunosuppressive therapy, except vitiligo or resolved asthma/atopy that is treated with broncho-dilators (e.g., albuterol). 14. Clinically significant, uncontrolled heart diseases: • Unstable angina within 6 months prior to screening • Myocardial infarction within 6 months prior to screening • History of documented congestive heart failure (New York Heart Association functional classification III-IV) • Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening • Ventricular arrhythmias • Supraventricular and nodal arrhythmias not controlled with medication • Other cardiac arrhythmia not controlled with medication • QTcF ≥ 450 ms (male patients), ≥ 460 ms (female patients) on the screening ECG (as mean of triplicate ECG)
Investigational and reference therapy	INC280 and PDR001
Efficacy assessments	Tumor assessment per RECIST v1.1 and per irRC.
Safety assessments	Incidence and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs), including changes in laboratory values, vital signs and Electrocardiograms (ECGs).
Other assessments	• Serum PK parameters [redacted] • Pharmacodynamic assessment on pre- and post-treatment newly obtained tumor samples
Data analysis	The study data will be analyzed and reported based on all patients' data of the phase Ib and phase II parts up to the time when all patients have completed at least nine cycles of treatment or discontinued the study.
Key words	Phase Ib/II, INC280, PDR001, checkpoint inhibitor, PD-1.

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Hepatocellular carcinoma (HCC) is the fifth most common form of cancer worldwide and the third most common cause of cancer-related deaths. HCC often occurs in the background of a cirrhotic liver. Most cases of HCC (approximately 80%) are associated with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections (Raza and Sood 2014, El-Serag 2011).

Other common etiologies include alcohol consumption, nonalcoholic steatohepatitis, exposure to carcinogens, and the genetic metabolic diseases such as hemochromatosis (El-Serag et al 2004, Donato et al 2002, Adams et al 2005, Turner et al 2002). Obesity has also been identified as an independent risk factor for developing HCC (Park et al 2010).

Approximately 80% of HCC patients present with advanced or unresectable disease (Ferlay et al 2010). Conventional chemotherapy has been proven to be ineffective for HCC (Llovet 2003, Yeo et al 2005). The Sorafenib HCC Assessment Randomized Protocol (SHARP) trial demonstrated that sorafenib, a multitarget tyrosine kinase inhibitor (TKI), was able to increase survival in patients with advanced HCC (stage C of the Barcelona Clinic Liver Cancer (BCLC) classification). Overall survival (OS) of 10.7 months was observed in the sorafenib arm vs 7.9 months in the placebo arm (Hazard Ratio (HR) = 0.69). The median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group ($p<0.001$) (Llovet et al 2008a). Improvement in OS for patients randomized to sorafenib in another phase III sorafenib study in the Asia-Pacific region was consistent with the SHARP trial (Cheng et al 2009). Sorafenib was approved as a standard first line systemic therapy for non-selected HCC patients with advanced disease. Although extended by sorafenib, time to progression (TTP) and overall survival (OS) remain limited as a result of de novo or acquired resistance (Bergers and Hanahan 2008, Paez-Ribes et al 2009).

Several compounds failed in the first or second line HCC setting (e.g. sunitinib, sorafenib in combination with erlotinib, and brivanib) and there is no approved standard of care for second-line treatment (Cheng et al 2011, Llovet et al 2012, Zhu et al 2012).

The management of HCC remains challenging as there is no therapeutic option available for patients with advanced HCC whose disease progressed while on or after treatment with sorafenib or who are intolerant to sorafenib treatment.

1.2 Introduction to investigational treatments

1.2.1 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 ATP competitive, reversible inhibitor of the cMET receptor tyrosine kinase.

INC280 dihydrochloride monohydrate is a slightly hygroscopic light yellow powder. The solubility of INC280 dihydrochloride at 25°C is approximately 3.47 mg/mL in water; 0.08 mg/mL in pH 6.8 and 0.72 mg/mL in pH 3.0 buffer.

[redacted]

Please refer to the [INC280 Investigator's Brochure] for more detailed information.

1.2.1.1 INC280 Non-clinical experience

1.2.1.1.1 *In vitro* and *in vivo* pharmacology

INC280 possesses potent inhibitory activity against the cMET kinase *in vitro* [inhibitory concentration (IC)50 = 0.13 ± 0.05 nM], and is highly specific for cMET with > 10,000-fold selectivity over several other human kinases tested. Potent activity of blocking cMET activation has been observed in cell-based biochemical and functional assays that measure cMET-mediated signal transduction, as well as cMET-dependent cell proliferation, survival, and migration.

In cMET–dependent mouse tumor models (including lung cancer models), INC280 exhibits dose-dependent antitumor activity and causes tumor regression at well tolerated doses that exceeded IC90 coverage (Liu et al 2011). Importantly, plasma levels of INC280 correlate with both the dose administered and the extent of tumor growth inhibition *in vivo*.

In cMET/HGF-driven mouse xenograft tumor models, oral dosing of INC280 demonstrated significant *in vivo* activity in blocking both cMET phosphorylation and tumor growth. Activation of cMET in such responsive models is either due to strong cMET overexpression (mostly as a consequence of gene amplification, e.g. in gastric or hepatocellular carcinoma) or hepatocyte growth factor (HGF) secretion resulting in an autocrine loop (e.g. in glioblastoma).

Collectively, the data suggest that INC280 possesses potent *in vitro* and *in vivo* biological and pharmacologic activities, and further support its clinical development as a potentially effective oral treatment for human cancers with cMET dysregulation.

1.2.1.1.2 Non clinical drug metabolism and pharmacokinetics summary

INC280 was absorbed rapidly in rats, dogs and monkeys. The absolute oral bioavailability following a single low dose was low in dogs (28%), and moderate to complete in rats and monkeys (> 66%).

INC280 plasma protein binding was moderate to high across species, and was 96% in humans with no concentration dependency. After oral dose of [^{14}C]INC280 in male pigmented and albino rats, INC280 and/or its metabolites were widely and rapidly distributed to all tissues. Melanin containing structures appeared to show specific uptake and prolonged retention of drug related material. INC280 can penetrate across the blood-brain barrier.

Metabolism is the predominant mechanism of elimination of INC280 in rats and monkeys after oral administration.

After single oral administration of [^{14}C]INC280 to rats and monkeys, the major portion of administered radioactivity was recovered in feces and only a minor fraction in urine. Direct renal excretion of INC280 was negligible and direct biliary excretion/intestinal secretion contributed only to a minor extent to the overall elimination of INC280.

[redacted]

1.2.1.1.3 Safety pharmacology and toxicology

A series of preclinical safety studies were completed to support human clinical trials with INC280, including safety pharmacology studies, genetic toxicology studies, general toxicology studies in rat and Cynomolgus monkey (up to 13 weeks in duration), and embryofetal developmental studies in rats and rabbits. Additionally, photosensitization potential was also assessed.

Safety pharmacology studies indicate that INC280 had no significant effects on central nervous system (CNS) and respiratory functions in rats, and no effects on cardiovascular function in monkeys.

Repeat-dose toxicity studies in rats and monkeys revealed the main target organs of toxicity: kidneys (monkeys only, crystalline-like material surrounded by multinucleated giant cells within the renal interstitium and/or tubular lumen), pancreas (both species, pancreatic acinar cell vacuolation and/or apoptosis, and elevations of amylase or lipase), CNS/brain (rats only, tremors and/or convulsions, white matter vacuolation in thalamus/caudate/putamen region), and the liver (both species, increase of serum enzymes).

In vitro and *in vivo* genetic toxicology studies indicate that INC280 did not induce mutations or cause chromosome aberrations.

Embryo-fetal studies in rats and rabbits indicate that INC280 is teratogenic to both species, thus INC280 should be considered potentially teratogenic to humans.

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

1.2.1.2 INC280 clinical experience

1.2.1.2.1 Clinical safety and tolerability

As of the cut-off date 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. Twenty one clinical studies are currently ongoing with INC280. A total of 19 patients have experienced 25 DLTs: 6 patients in single agent studies and 13 in combination studies.

Overall, the majority of the reported adverse events (AEs) have been of mild or moderate 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 peripheral edema (77 patients, [35.0%]), nausea (69 patients, [31.4%]), vomiting (40 patients, [18.2%]), increased blood creatinine (39 patients, [17.7%]), and fatigue (34 patients, [15.5%]), the majority Grade 1/2. The most frequently occurring Grade 3/4 AEs suspected to be related to INC280 as a single agent included peripheral edema and increased lipase (each in 9 patients, [4.1%]), fatigue (8 patients, [3.6%]), increased alanine aminotransferase (7 patients, [3.2%]), increased 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 abnormal liver function test 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 was suspected to

[redacted]

be related to the combination of INC280 plus gefitinib. The patient permanently discontinued both study drugs. Liver function tests improved after treatment discontinuation. Hepatotoxicity could not be attributed solely to either drug alone or to the combination.

As of the IB cut-off of 28-Sep-2017, pneumonitis and ILD have been reported from both INC280 single agent and combination studies with the EGFR TKIs, including events with fatal outcome. Investigators are advised to carefully monitor patients for signs and symptoms of pneumonitis and implement dose modification and follow up evaluations described in the protocol in all INC280 studies, both single agent and in combination studies.

The maximum tolerated dose (MTD) for INC280 capsules or tablets as single agent was not reached. The recommended phase II dose (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. In this study, INC280 tablets will be used.

1.2.1.2.2 Clinical pharmacology

As of 28-Sep-2017, INC280 (capsule and tablet) single agent steady state pharmacokinetic (PK) data are available from five single agent and four combination studies. INC280 was rapidly absorbed after oral administration in humans. The median time to reach the maximum drug concentration (Tmax) ranged from 1 to 2 hours for tablets and 1 to 4 hours for capsules. The elimination half-life (T1/2) estimated from [CINC280X1101] ranged from 3.5 to 6.3 hours across the cohorts. Accumulation of 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 MF (market form) tablet formulation to INC280 capsule formulation. The outcome of this study showed that tablets provided higher systemic exposures (Cmax and AUC) and lower inter-subject variability in healthy subjects. 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. 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.

INC280 displayed pH-dependent solubility *in vitro*. Daily treatment with 20 mg rabeprazole (a long proton pump inhibitor) 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 ([CINC280A2101]). 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 ([CINC280X2107]). Preliminary pharmacokinetics data from the ongoing study [CINC280A2108] in 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

[redacted]

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.

Several studies were conducted to assess the DDI between INC280 and concomitant medications. As a potential perpetrator, [CINC280A2103] showed that multiple doses of INC280 tablets at 400 mg BID did not lead to clinically significant increase of CYP3A4 substrate (midazolam) exposure. However, AUC of CYP1A2 substrate (caffeine) was increased by 135%. Therefore, INC280 is not a CYP3A4 inhibitor, but a moderate CYP1A2 inhibitor. In addition in study [CINC280A2105], multiple doses of INC280 tablets at 400 mg BID led to a 74% increase in digoxin (P-gp substrate) Cmax and a 47% increase in AUC, and a 204% and 108% increase in rosuvastatin (BCRP substrate) Cmax and AUC, respectively. Therefore, INC280 is an inhibitor of P-gp as well as BCRP transporters, with clinically relevant DDI potential.

As a potential causative agent, in study [CINC280A2102], when co-administered with itraconazole, INC280 AUC increased by approximately 40% while there was no change in Cmax. When co-administered with rifampicin, INC280 AUC and Cmax decreased by approximately 66% and 56%, respectively.

INC280 does not show a risk of QT prolongation. Preliminary analysis on 110 patients in study [CINC280A2201] showed that no patients had new post-baseline QTcF values greater than 500 ms. 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.

An exploratory population PK (PopPK) analysis indicated that the INC280 exposure in HCC patients in those studies was similar to those in non-HCC-patients.

For more information, please refer to the most updated version of the [INC280 Investigator's Brochure].

1.2.2 Overview of PD-1 and PDR001

PD-1 is a critical checkpoint receptor that is expressed by effector T cells upon activation (Okazaki et al 2013). It is also expressed by B cells, natural killer T (NKT) cells, CD4+ regulatory T (Tregs) cells, and some dendritic cells (DC) subsets upon activation (Francisco et al 2010). Its ligands, Programmed Death-Ligand 1 (PD-L1) and Programmed Death-Ligand 2 (PD-L2) are expressed by dendritic cells, macrophages and monocytes, and can be induced on virus-infected cells and many types of tumors (Keir et al 2008). Engagement of PD-1 with its ligands PD-L1 and PD-L2 negatively regulates effector T cell signaling and function and protects the tumor cells from the induction of apoptosis by effector T cells.
The PD-1/PD-L1 axis is exploited by many tumor types to avoid detection by the adaptive immune system (Murphy 2011). Blockade of the PD-1 pathway has been shown to lead to increased numbers of effector T cells through induction or expansion and improved cytolytic activity towards tumors. Additionally, PD-1 blockade is associated with accumulation of effector T cells and a reduced number of Tregs at the tumor site (Wang et al 2009, Mangsbo et al 2010, Mkrtichyan et al 2011, Rosenblatt et al 2011).

[redacted]

Both preclinical and clinical studies have demonstrated that anti-PD-1 blockade restores activity of "exhausted" effector T cells and results in robust anti-tumor response. Clinical data with other anti-PD-1 antibodies have demonstrated that PD-1 checkpoint inhibition results in clinically relevant anti-tumor activity in a variety of solid tumors, including melanoma, non-small cell lung carcinoma (NSCLC), renal cell cancer (RCC) and head and neck squamous cell cancer (HNSCC) (Topalian et al 2012, Hamid et al 2013, Topalian et al 2014, Lyford-Pike et al 2013).

PDR001 is a high-affinity, ligand-blocking, humanized anti-PD-1 IgG4 antibody (stabilized hinge, S228P) which blocks the binding of PD-L1 and PD-L2 to PD-1. PDR001 is cynomolgus monkey cross-reactive and shows functional activity *in vitro* and *in vivo*.

1.2.2.1 PDR001 Non-clinical experience

PDR001 binds specifically and with high affinity to human PD-1 and shown to enhance the interleukin-2 production in *ex vivo* lymphocyte stimulation assays. Repeat administration of PDR001 to monkeys was well tolerated at all doses tested in the GLP toxicology study. No test article-related in-life, mortality, organ weight changes, or macroscopic findings were noted. There were no PDR001-related effects seen in any of the safety pharmacology endpoints assessed (cardiovascular, neurobehavioral, and respiratory). Macrophage infiltrates into the splenic white pulp were observed in animals given 100 mg/kg/week and mononuclear cell infiltrates, often associated with fibrosis, around the injection site blood vessel (saphenous vein) in a few animals given ≥25 mg/kg/week. These PDR001-related microscopic changes were fully reversible after an eight week recovery. Additionally, mostly low grade mononuclear infiltrates in the vascular and perivascular space in several tissues of main and recovery treated animals and in recovery controls but with a slightly higher incidence in treated animals. No evidence of parenchymal damage was associated with the vascular/perivascular changes in any of the organs examined and the changes were not associated with any frank tissue injury.

The Highest Non-Severely Toxic Dose (HNSTD) dose in this study was 100 mg/kg. PDR001 has a favorable safety profile in monkeys that supported a projected human starting dose of 1 mg/kg in the first in human study [CPDR001X2101].

1.2.2.2 PDR001 Clinical experience

PDR001 is currently being tested in a multi-center, open-label study starting with a phase I dose escalation part followed by a phase II part. The [CPDR001X2101] study started enrollment on 27 April 2015 and is ongoing. As of 17 December 2015, a total of 58 patients had been treated in the study at the dose levels of 1, 3 and 10 mg/kg Q2W and 3 and 5 mg/kg Q4W. No patient experienced a DLT and the toxicity profile appears to be similar to that of marketed inhibitors of PD-1. The PK data obtained from the dose escalation, and modeling of the exposure data, support the use of flat dosing for PDR001 of 400 mg given every 4 weeks. The expected PDR001 Ctrough concentrations are in line with observed steady state mean Ctrough concentrations for pembrolizumab, which is approved with substantial efficacy in several cancer types. The data also support the use of 300 mg Q3W as an alternative dose regimen if it is more convenient for scheduling purposes, for example in combination treatment regimens.

It is also within the objective of the phase II part of the [CPDR001X2101] study to assess PDR001 anti-tumor activity in various advanced solid tumors including the "benchmark

diseases" such as NSCLC and melanoma, where response rates to nivolumab and pembrolizumab are known.

For further details, please refer to the [PDR001 Investigator's Brochure].

1.2.3 Overview of INC280 and PDR001

1.2.3.1 Non-clinical and clinical experience with the combination of INC280 and PDR001

As of 27-Mar-2018, a total of 27 patients had been treated with INC280 in combination with PDR001 in the dose escalation part of the study, at dose levels of 200 mg INC280 BID, 300 mg INC280 BID, and 400mg INC280 BID, all in combination with 300 mg PDR001 Q3W.

2 Rationale

2.1 Study rationale and purpose

HCC is associated with high mortality and morbidity due to the limited efficacy of the current available treatment in this population. For patients who were treated with sorafenib and discontinued treatment due to disease progression or intolerability, there is no standard approved therapy as outlined in Section 1.

cMET overexpression has been associated with increased vascular invasion, resistance to chemo- and radiotherapy, and poor clinical outcome in HCC (Boix et al 1994, Suzuki et al 1994, Ueki et al 1997, Tavian et al 2000, Kaposi-Novak et al 2006, Liu et al 2008). Tissue localization studies of HGF and cMET protein support the existence of both autocrine and paracrine mechanisms of action of HGF in HCC (Ljubimova et al 1997, Luo et al 1999). Targeting the disease through a different class of drugs might be beneficial to these patients with no standard of care available.

INC280 has shown anti-tumor activity in several pre-clinical models of HCC that are driven either by cMET gene amplification or by HGF stimulation. Autocrine or paracrine activation of cMET by HGF was found to drive growth and migration of HCC cell lines *in vitro* (Xie et al 2001). Paracrine stimulation of cancer cells by HGF originating from non-cancerous liver tissue that could promote growth and metastasis was reported (Wu et al 2006). Preclinical studies performed at Novartis have shown that HGF overexpression is found in almost all liver tissue samples adjacent to HCC tumors and that cMET is expressed by the majority of HCC tumors. Functional studies showed that knockdown of cMET by adenovirus-delivered siRNA inhibited growth of HCC lines with particularly high cMET expression *in vitro* and *in vivo* (Zhang et al 2005), underlining the potential of activated cMET to drive liver carcinogenesis.

The recently reported positive results (TTP and OS advantage: HR=0.43, p=0.03; HR=0.38, p=0.01 respectively) of tivantinib (cMET inhibitor) in the treatment of HCC provide a strong rationale for the evaluation of cMET targeted agents in HCC (Santoro et al 2012).

Low expression of programmed cell death 1 ligand 1 (PD-L1) in combination with high human leucocyte antigen (HLA) class 1 expression was found to be prognostic for improved outcomes

[redacted]

in HCC patients (Umemoto et al 2014), suggesting that novel therapies targeting the PD-L1/PD-1 pathway may thus show therapeutic benefit in HCC.

Recently, a phase I/II study in advanced HCC (El-Khoueiry et al 2015) showed that Nivolumab monotherapy has a manageable safety profile, including in patients with HBV and HCV infections. Durable responses were observed across all dose levels and etiologic cohorts. 7 out of 8 tumor responses occurred within three months of starting study treatment and 6 out of 8 patients had ongoing responses after several months of study treatment. The 12-month overall survival rate was 62%.

In conclusion, the purpose of this phase Ib/II study is to determine in the phase Ib part the MTD/RP2D for the combination treatment of INC280 plus PDR001 and to further assess in the phase II part the safety and clinical activity of both INC280 in combination with PDR001, and single agent PDR001 in patients with advanced HCC with cMET dysregulation, who experienced progression during or after discontinuation of sorafenib treatment, or intolerance to sorafenib treatment.

2.2 Rationale for the study design

This is an open-label, multicenter, randomized and controlled phase Ib/II study of INC280 in combination with PDR001 or PDR001 single agent in patients with advanced HCC, who experienced progression during or after discontinuation of sorafenib treatment, or intolerance to sorafenib treatment.

Phase Ib part

The phase Ib part of the study is a dose escalation of INC280 in combination with PDR001. Cohorts of patients will receive escalating doses of INC280 combined with a fixed dose of PDR001 until MTD/RP2D is reached. The MTD/RP2D will be determined from the collective experience in the clinic considering the safety data, pharmacokinetic data, pharmacodynamic data and any early anti-tumor activity observed along with the statistical inference from the Bayesian logistic regression model (BLRM).

This open-label dose escalation study design using a BLRM is a well-established method to estimate the MTD/RP2D in cancer patients. The adaptive BLRM will be guided by the Escalation with Overdose Control (EWOC) principle to control the risk of DLT in future patients on study. The use of Bayesian response adaptive models for small datasets has been accepted by European Medicines Agency (Guideline on clinical trials in small populations, 13-Feb-2007) and endorsed by numerous publications (Zacks et al 1998, Neuenschwander et al 2010, Neuenschwander et al 2014), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative.

Phase II part

A randomized controlled design for the phase II part is appropriate to assess clinical activity of INC280 in combination with PDR001 versus PDR001 single agent. This design is stratified by region (Asian vs. non-Asian).

[redacted]

The phase II part of the study will begin after the MTD/RP2D is determined. Patients will be randomized 1:1 to treatment INC280+PR001 or PDR001 single agent with the stratification factor of region (Asian vs. non-Asian). The cMET status will be assessed retrospectively, after randomization.

2.2.1.1 Rationale for including cMET high patients

High cMET expression is defined as either IHC 3+ in at least 50% of tumor cells, or IHC 2+ in at least 50% of tumor cells and at the same time a gene copy number (GCN) of at least 5 (which is considered as evidence for cMET gene amplification (Schildhaus et al 2012).

As of 28-Oct-2015, 28 HCC patients have been treated in the phase II part of study [CINC280X2201] of INC280 single agent in first line HCC. Among the eight cMET high patients, three out of the eight HCC patients treated with INC280 capsules at the dose level of 600 mg BID (RP2D with INC280 capsules) achieved a confirmed partial response (cPR), lasting for 5 (discontinuation due to patient's decision), 7.5+ (ongoing) and 5+ (ongoing) months respectively.

The preliminary efficacy data clearly suggest that patients with cMET high HCC may obtain therapeutic benefit from treatment with single agent INC280, including long lasting responses.

In addition to the well-documented role of cMET in cancer cell autonomous survival and growth, evidence is emerging to suggest that cMET activation could also have a profound effect on tumor immune-tolerance, at least partially through the direct induction of negative co-stimulatory molecule PD-L1 in the cancer cell. Balan and colleagues have demonstrated that cMET is co-expressed with PD-L1 in renal cell carcinoma and elucidated that PD-L1 expression is a direct consequence of the transcriptional regulation downstream of cMET (Balan et al 2015).

Beyond oncogenic genetic aberrations of the cMET pathway in cancer cells, the canonical autocrine/paracrine effects of HGF, which could be produced either by HCC or liver stroma cells, also play an important role in the regulation of the inflammatory process. HGF alters the antigen-presenting function and differentiation of DCs and macrophage and subsequently may negatively impact T cells and thus INC280 might restore immune cell functions by preventing/reducing the HGF signaling (Molnarfi et al 2015).

Blockade of the PD-1 pathway has demonstrated preliminary clinical efficacy with durable responses in second line HCC (El-Khoueiry et al 2015), leading to a phase III study of nivolumab against sorafenib in 1st Line HCC (https://clinicaltrials.gov/ct2/show/NCT02576509).

In conclusion, in cMET high HCC patients, PDR001 single agent should provide a clinical benefit similar to Nivolumab; while the combination of PDR001 + INC280 should provide additional clinical benefit mediated by:

- INC280 which inhibits any suppressive effects of HGF on cells of the immune system such as dendritic cells and potentially a cMET pathway inhibition in cancer cells.
- PDR001 which blocks the PD-1 pathway triggering a better immune response that might result in durable anti-tumor responses.

[redacted]

2.2.1.2 Rationale for including cMET low patients

As of 28-Oct-2015, 20 patients with cMET low (IHC 2+/GCN <5 or IHC 1+/any FISH) were treated with INC280 600 mg BID (capsules). No response was reported and the stable disease (SD) rate at 9 weeks was 25% (5/20 patients).

Although in cMET low HCC the direct impact of the cMET pathway in cancer cell is less clear (see Section 2.2.1.1), HGF produced by HCC and liver stroma cells might alter the antigen-presenting function and differentiation of dendritic cells and macrophage and subsequently may negatively impact the T cells and thus might reduce the capacity of the immune system to react against cancer cells (Molnarfi et al 2015).

In cMET low HCC patients, PDR001 single agent should provide a clinical benefit similar to Nivolumab (El-Khoueiry et al 2015). The combination of INC280 + PDR001 should provide a sustained clinical benefit mediated by:

- INC280 which inhibits any suppressive effects of HGF on cells of the immune system such as dendritic cells and potentially a cMET pathway inhibition in cancer cells (cMET/HGF dependency less clear)
- PDR001 which blocks the PD-1 pathway triggering a better immune response resulting in anti-tumor activity.

2.3 Rationale for dose and regimen selection

This is the first study evaluating the combination of INC280 and PDR001. In order to understand the safety, tolerability and PK of the combination, starting doses for the combination of INC280 and PDR001 are planned as 200 mg BID and 300 mg Q3W, respectively. The PDR001 dose will remain constant during the phase Ib and phase II part.

To date, PDR001 has been tested up to 10mg/kg every 2 weeks which was not considered an MTD dose. RP2D from the ongoing [CPDR001X2101] study is 300 mg given every 3 weeks. The PDR001 exposure at this dose regimen is expected within the range of those observed in the CPDR001X2101 study with no DLTs. In addition, the expected PDR001 Ctrough concentrations are in line with observed mean steady state Ctrough concentrations for Pembrolizumab. In accordance with clinical experience of nivolumab and pembrolizumab (Topalian et al 2012, Topalian et al 2014, Hamid and Carvajal 2013, Robert et al 2014), PDR001 is expected to demonstrate antitumor activity at 300 mg dosed every 3 weeks.

INC280 tablet 400 mg BID is the RP2D selected in phase I and phase II single agent studies (including in the first line HCC patients), as well as in combination with gefitinib. For the dose escalation phase of this study, the starting dose of INC280 will be 200 mg BID, which is two dose levels below the RP2D of 400 mg BID. Strong pharmacokinetic drug-drug interaction is not expected between INC280 and PDR001. However as INC280 metabolism is moderately mediated by CYP3A4/5 and PDR001 treatment might have impact on metabolizing enzymes through cytokine regulation, INC280 exposure will be monitored in the dose escalation phase to assess drug-drug interaction (DDI).

[redacted]

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.3
Phase Ib part: To characterize the safety and tolerability of INC280 in combination with PDR001 and identify the MTD and/or RP2D	Phase Ib part: Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs. Incidence of DLT during the first 2 cycles of treatment. Tolerability: Dose interruptions, reductions, and dose intensity	
Phase II part: - To compare the efficacy of INC280 in combination with PDR001 vs. PDR001 single agent	Phase II part: Overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1)	
Secondary		Refer to Section 10.4
Phase Ib/II part: To further characterize the efficacy of INC280 in combination with PDR001 and PDR001 single agent	Best overall response (BOR), duration of overall response (DOR), time to response (TTR), progression-free survival (PFS), time to progression (TTP), overall survival (OS), and for phase Ib: Overall response rate (ORR)	
Phase II part: To characterize the safety and tolerability of INC280 in combination with PDR001 and PDR001 single agent	Safety: Incidence and severity of adverse events (AEs) and serious adverse events, including changes in laboratory parameters, vital signs and electrocardiograms (ECGs) Tolerability: Dose interruptions, reductions and dose intensity	

[redacted]

Objective	Endpoint	Analysis
Phase Ib/II parts: To characterize the pharmacokinetic profile of INC280 in combination with PDR001 and PDR001 single agent	Plasma/serum PK parameters (e.g., AUC, Cmax, Tmax) Plasma/serum concentration vs. time profiles	
Phase Ib/II parts: To assess the pharmacodynamic effect of INC280 in combination with PDR001 and PDR001 single agent in tumor biopsy	TIL characterization & CD8 and PD-L1 protein expression	

[redacted]

4 Study design

4.1 Description of the study design

This is a phase Ib/II, open label, multicenter study starting with a phase Ib dose escalation part followed by a randomized phase II part. INC280 will be administered orally twice daily and PDR001 will be administered i.v. every three weeks until a patient experiences unacceptable toxicity, progressive disease as per irRC and/or treatment is discontinued at the discretion of the investigator or the patient. Patients should not discontinue treatment based on progressive disease per RECIST unless clinical deterioration or increase in tumor markers is observed. The study design is summarized in Figure 4-1.

Phase Ib dose escalation part

During the phase Ib part of the study, cohorts of patients will be treated with INC280 in combination with a fixed dose of PDR001 until the MTD is reached or RP2D is established. The INC280 dose will be increased and the PDR001 dose will remain constant. The dose escalation will be guided by a BLRM following the EWOC principle. A minimum of 12 patients are required during dose escalation to determine the MTD of INC280 in combination with PDR001. If a recommended phase II dose is identified without determination of the MTD, fewer than 12 patients may be required (for further details see Section 6.2.3).

Phase II part

Once the MTD and/or RP2D have been declared for INC280 in combination with PDR001, additional patients will be enrolled in the phase II part in order to assess the anti-tumor activity of INC280 in combination with PDR001 and PDR001 single agent.

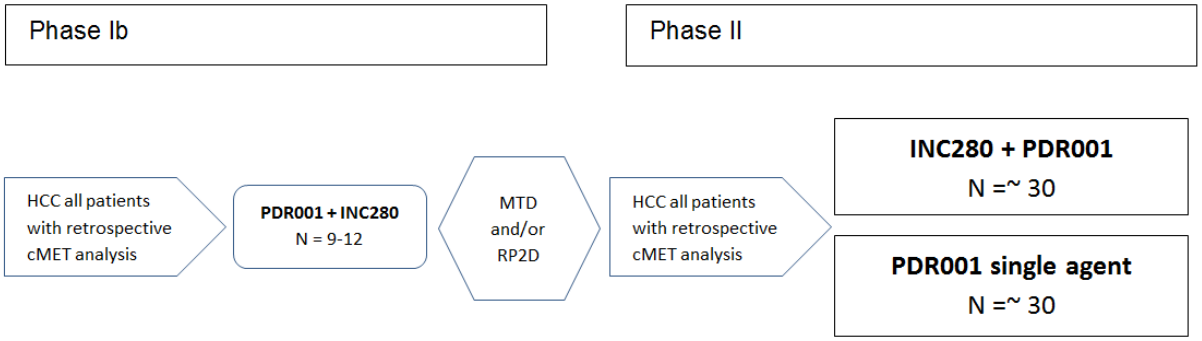
In total, approximately 60 patients will be enrolled. Patients will be randomly assigned, in a 1:1 ratio, to treatment with either INC280 in combination with PDR001 or PDR001 single agent.

Considering that the treatment guidance for HCC (specifically the locoregional treatments such as percutaneous hepatic arterial embolization, radiofrequency ablation, and percutaneous interventional therapy) are different in various parts of the world reflected in the difference in OS and TTP results observed in the SHARP study and the Asia-Pacific sorafenib studies (Llovet et al 2008b, Cheng et al 2009, Lencioni et al 2012, Johnson et al 2013), the randomization for treatment assignment in this study will be stratified by geographical region (Asian vs. non-Asian).

Analysis for cMET status will be performed after randomization.

[redacted]

Figure 4-1 Study Design



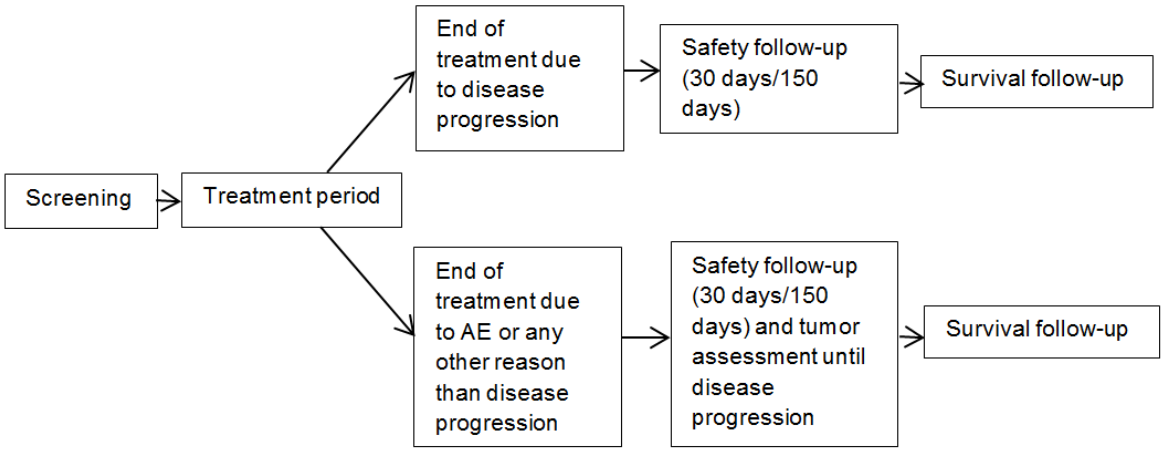
A complete cycle of treatment is defined as 21 days of twice daily treatment with INC280 and the DLT period in the phase Ib part as 2 cycles.

This study will use a Novartis Interactive Response Technology (NIRT) system for randomization and management of INC280 and PDR001 study drug (see Section 6.6.2).

Study flow

The study is comprised of 3 periods: Screening, Treatment, Follow-up period (150-day Safety for PDR001 and 30-day for INC280 (in case PDR001 has been discontinued > 120 days before), Disease Progression and Survival. Patients will undergo safety and efficacy assessments during screening and periodically during treatment and follow-up as outlined in Table 7-1.

Figure 4-2 Study Flow



4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned. However, in the phase I part, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study (see Section 10.6).

[redacted]

4.3 Definition of end of the study

The end of the study will be when:

- A minimum of 80% of patients have died, have been lost to follow-up, or have been followed for a minimum of 18 months after the first dose of study treatment, and all patients have completed treatment and the safety follow-up period

or

- the study is terminated early

or

- another clinical study becomes available that can continue to provide study treatment in this patient population, all patients ongoing transferred to that clinical study and all discontinued patients have completed the safety follow-up period. The follow-up for disease progression and survival will not be performed or pursued (see Section 7.1.5).

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative treatment option to patients who, in the opinion of the investigator, are still deriving clinical benefit.

The disease and survival follow-up evaluations might not be completed in case Novartis decides to stop enrollment prematurely. In such cases, end of study will be upon the Study Evaluation Completion (SEC) or the last patient treated, including the completion of the safety follow-up period.

See Section 10 Statistical Methods and Data Analysis 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 for End of Treatment (EOT) visit and the assessments for EOT should be performed as described in Section 7.1.3 and Section 7.1.4 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 Institutional Review Boards (IRBs) and/or independent ethics committees (IECs) of the early termination of the trial.

5 Population

5.1 Patient population

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

[redacted]

The Investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria 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 procedures that are not considered standard of care. [For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.]
2. Age ≥ 18 years.
3. Histologically or cytologically documented locally advanced recurrent or metastatic HCC or for patients with cirrhosis clinical diagnosis of HCC according to the American Association for the Study of Liver Diseases (AASLD) and Asian Pacific Association for the Study of the Liver (APASL) criteria. Current cirrhotic status of Child Pugh Class A (5-6 points), with no encephalopathy and/or clinically significant ascites (defined as requiring the use of diuretics or paracentesis treatment). Child Pugh status (see Appendix 7) must be calculated based on clinical and laboratory results during the screening period.
4. Baseline tumor tissue (newly obtained) must be available at screening. Patient must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution's guidelines and requirements for such procedure.
5. Patients must be willing to undergo a new tumor biopsy during the study (6 to 9 weeks after start of study treatment, if medically feasible). For patients in the phase II part of the study, exceptions may be granted after documented discussion with Novartis. After a sufficient number of paired biopsies are collected, the decision may be taken to stop collecting the biopsies.
6. Patients must have received prior systemic sorafenib treatment for HCC with documented progression during or after discontinuation of sorafenib treatment (for France only: patients must have received at least 8 weeks of prior sorafenib treatment), or are intolerant to sorafenib (defined as documented Grade 3 or 4 adverse events that led to sorafenib discontinuation).
7. ECOG Performance Status ≤ 1.
8. Willing and able to swallow and retain oral medication.
9. The last dose of sorafenib must have been given ≥ 2 weeks prior to mandatory tumor biopsy at baseline.
10. At least 1 measurable lesion as per RECIST v1.1 present at screening (progressing or new since last anti-tumor therapy). Lesions previously treated with local therapy, such as radiation therapy, hepatic arterial embolization, radiofrequency ablation, and percutaneous interventional therapy should not be selected unless progression is noted at baseline, in which case, these lesions would be considered as non-target lesions.
11. Patients must be tested during screening for Hepatitis-B-Virus surface antigen (HbsAg) status. Patients are included in the study if they have adequately controlled hepatitis B, defined by:
    - receiving a nucleoside analog anti-viral drug for 3 or more months, and

[redacted]

- serum hepatitis B virus (HBV) deoxyribonucleic acid (DNA) level of less than 100 IU/ml via polymerase chain reaction quantification assays prior to enrollment.

12. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

5.3 Exclusion criteria

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

1. Patient has received the following therapies prior to the first dose of study treatment:
   - Previous systemic anti-cancer therapy (including therapeutic cancer vaccines and immunotherapeutics) other than sorafenib (sorafenib must be completed within > 2 weeks prior to the first dose of study treatment) or INC280.
   - Previous locoregional therapy (e.g. hepatic arterial embolization, radio-frequency ablation, radiation therapy) if:
     - administered after sorafenib treatment with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain. Loco regional therapy for the focally painful liver tumor mass will be discussed on a case by case with Novartis.
     - completed within 4 weeks prior to the dosing and, if present any related acute toxicity grade > 1.
2. Use of any live vaccines within 4 weeks of initiation of study treatment.
3. Major surgery within 2 weeks of the first dose of study treatment (mediastinoscopy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery).
4. Patients potentially candidate for any loco regional treatment (e.g. hepatic resection, hepatic arterial embolization).
5. Participation in an interventional, investigational study within 2 weeks of the first dose of study treatment, unless agreed otherwise with Novartis.
6. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
7. Presence of CTCAE grade ≥ 1 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if CTCAE grade ≥ 3) due to prior cancer therapy, unless documented agreement with Novartis.
8. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) ≤ 2 weeks prior start or study drug. An erythroid stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the patient is on a stable dose.
9. Presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or corticosteroids within 2 weeks of the first dose of study treatment.
10. Systemic chronic steroid therapy or any immunosuppressive therapy (≥ 10mg/day prednisone or equivalent). Topical, inhaled, nasal and ophthalmic steroids are allowed.
11. Interferon use within 2 weeks of the first dose of study treatment.

[redacted]

12. History of severe hypersensitivity reactions to other mAbs.
13. History of HCC tumor rupture.
14. Positive human immunodeficiency (HIV) testing at screening or known history of testing positive for HIV or known acquired immunodeficiency syndrome.
15. History of organ transplant.
16. Clinically significant pleural effusion that either required pleurocentesis or is associated with shortness of breath.
17. Any other condition that would, in the Investigator's judgment, contraindicate patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures.
18. Patients receiving treatment with medications that are strong inducers of CYP3A4 and that cannot be discontinued at least 1 week prior to the start of treatment with INC280 and for the duration of the study. Refer to Appendix 5.
19. Unable to stop herbal/food supplements or treatments which are considered to be capable of significantly causing either PK or PD herb/food-drug interactions. From a PK point of view, refer to Appendix 5. From a PD point of view, this definition includes any health authority approved herbal medication for HCC.
20. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of INC280 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
21. Patient having out of range laboratory values defined as:
    - Total bilirubin > 2 mg/dL, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
    - Alanine aminotransferase (ALT) > 5 x ULN
    - Aspartate aminotransferase (AST) > 5 x ULN
    - Coagulation: Prothrombin Time (PT) > 4 seconds more than the ULN or International Normalized Ratio (INR) > 1.7
    - Absolute neutrophil count (ANC) < 1.5 x 10^9/L
    - Platelet count < 75 x 10^9/L
    - Hemoglobin < 9 g/dL
    - Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 45 mL/min
    - Asymptomatic serum amylase 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.)
    - Serum lipase > ULN
    - Potassium, Magnesium, Phosphorus, total Calcium (corrected for serum albumin) outside of normal limits (patients may be enrolled if corrected to within normal limits with supplements during screening)
22. Active autoimmune disease or a documented history of autoimmune disease, including ulcerative colitis and Crohn's disease or any condition that requires systemic steroids or

[redacted]

any immunosuppressive therapy, except vitiligo or resolved asthma/atopy that is treated with broncho-dilators (e.g., albuterol).

23. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; and completely resected carcinoma in situ of any type.
24. Clinically significant, uncontrolled heart diseases.
    - Unstable angina within 6 months prior to screening
    - Myocardial infarction within 6 months prior to screening
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening
    - Ventricular arrhythmias
    - Supraventricular and nodal arrhythmias not controlled with medication
    - Other cardiac arrhythmia not controlled with medication
    - QTcF ≥ 450 ms (male patients), ≥ 460 ms (female patients) on the screening ECG (as mean of triplicate ECG)
25. Pregnant or 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.
26. 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 150 days after the last dose of PDR001 and 7 days after the last dose of INC280 (in case PDR001 was discontinued > 150 days before). Highly effective contraception methods include:
    - 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
    - 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
    - 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.
    - Use of oral, injected or implanted hormonal methods of contraception or placement if 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.

[redacted]

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.

27. Sexually active males must use a condom during intercourse while taking INC280 and for 7 days after the last dose of INC280 and 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.

6 Treatment

6.1 Study treatment

For this study, the **investigational drugs** are INC280 and PDR001. The study treatment is defined as INC280 in combination with PDR001 or PDR001 single agent.

All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded on the Dosage Administration Record (DAR) eCRF page.

6.1.1 Dosing regimen

Table 6-1 Starting dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Starting dose	Frequency and/or Regimen
INC280	FMI tablets for oral use	200mg	Twice daily (BID) on a continuous schedule
PDR001	Powder for solution for i.v. infusion	300mg	Every 3 weeks (Q3W)

INC280

INC280 tablet will be administered orally on a continuous twice daily (BID) dosing schedule, on a flat scale of mg/day and not individually adjusted by weight or body surface area. The Investigator must instruct the patient to take the study drug exactly as prescribed.

- Except on days of PK sampling, patients should take INC280 tablets twice daily (BID) at approximately the same time each day starting at Cycle 1 Day 1.
- Each dose of INC280 is to be taken with a glass of water (at least 8 ounces – approximately 250 mL) and consumed over as short a time as possible (i.e., not slower than 1 tablet every 2 minutes).
- Patients should be instructed to swallow the tablets whole and not to chew them.
- INC280 may be administered with or without food. The morning and the evening doses should be taken 12 (± 4) hours apart, although 12-hour interval is highly recommended. If

[redacted]

a dose is not taken within 4 hours of the planned dosing time, the missed dose should not be replaced.

- On days when PK blood samples are to be collected, patients will be instructed to hold their dose until arrival at the study center. INC280 will be administered at the site in the morning. The exact time of drug administration should be recorded in the appropriate eCRF. The PK blood draws will be supervised by a member of the research team. If a patient vomits within 4 hours of INC280 dosing, the time of vomiting should be recorded on the eCRF.
- Patients should be instructed not to make up for missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 4 hours of the scheduled twice daily dosing. If that occurs, then the dose (or part remaining dose) should not be taken and dosing should restart with the next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose.
- During the whole 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 solarium).
- All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the DAR eCRF page.

PDR001

PDR001 will be administered via i.v. infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 3 weeks. PDR001 may be delayed due to toxicities. The PDR001 dosing may resume once the adverse event has resolved to grade 1 or baseline, and the start of the cycle will be shifted accordingly.

Sequence of INC280 and PDR001 treatment

INC280 will be administered prior to PDR001 along with its pre-medication (if pre-medication is necessary). The sequence will allow consistent time of daily dosing for INC280. A minimum of 1 hour must pass from the time of INC280 (morning dose) administration to the administration of PDR001.

6.1.2 Ancillary treatments

Patients should not receive pre-medication to prevent infusion reaction before the first infusion of PDR001, in order to determine if pre-medication is necessary. If a patient experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a patient experiences a Grade 3 anaphylactic/anaphylactoid reaction, the patient will discontinue study treatment. The patient may resume study treatment following documented discussion with Novartis.

[redacted]

Patients should be treated in a facility equipped for cardiopulmonary resuscitation. Appropriate resuscitation equipment should be available at the bedside and a physician readily available.

Guidelines on management of PDR001 infusion reactions are provided in Section 6.3.2, Table 6-4 and Appendix 4.

The CTCAE category of "Infusion related reaction" should be used to describe PDR001 infusion reactions, unless the Investigator considers another category, such as "Allergic reaction," "Anaphylaxis," or "Cytokine release syndrome" more appropriate in a specific situation.

6.1.3 Treatment duration

All patients will begin treatment on Cycle 1 Day 1. Patients may be discontinued from treatment with the study drug due to:

- unacceptable toxicities
- confirmed disease progression per irRC
- at the discretion of the Investigator (e.g. clinical deterioration)
- patient's decision.

Note: Patients will not be withdrawn from the study due to progressive disease per RECIST v1.1. Please refer to Section 7.1.3 and Section 7.1.4 for further details.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

This is the first study evaluating the combination of INC280 and PDR001. In order to understand the safety, tolerability and PK of the combination, starting doses for the combination of INC280 and PDR001 are planned as 200 mg BID and 300 mg Q3W, respectively. The PDR001 dose will remain constant during the phase Ib and phase II part.

To date, PDR001 has been tested up to 10mg/kg every 2 weeks which was not considered an MTD dose. RP2D from the ongoing [CPDR001X2101] study is 300 mg (3.75mg/kg) given every 3 weeks. The PDR001 exposure at this dose regimen is expected within the range of those observed in the [CPDR001X2101] study with no DLTs. It is expected to achieve mean steady state Ctrough concentrations that are >70-fold higher than the *in vitro/ex vivo* potency EC50 for PDR001 (assessed as 0.42 µg/mL). In addition, the expected PDR001 Ctrough concentrations are in line with observed mean steady state Ctrough concentrations for Pembrolizumab. In accordance with clinical experience of nivolumab and pembrolizumab (Topalian et al 2012, Topalian et al 2014, Hamid and Carvajal 2013, Robert et al 2014), PDR001 is expected to demonstrate antitumor activity at 300 mg dosed every 3 weeks.

INC280 tablet 400 mg BID is the RP2D selected in phase I and phase II single agent studies (including in the first line HCC patients), as well as in combination with gefitinib. For the dose escalation phase of this study, the starting dose of INC280 will be 200 mg BID, which is two dose levels below the RP2D of 400 mg BID. Strong pharmacokinetic drug-drug interaction is not expected between INC280 and PDR001. However as INC280 metabolism is moderately mediated by CYP3A4/5 and PDR001 treatment might have impact on metabolizing enzymes

[redacted]

through cytokine regulation, INC280 exposure will be monitored in the dose escalation phase to assess DDI.

6.2.2 Provisional dose levels

Table 6-2 describes the starting dose for the phase Ib part and the dose levels that may be evaluated during this trial. PDR001 dose will be a fixed dose and only INC280 will be escalated.

Table 6-2 Provisional dose levels (Phase Ib part – INC280 in combination with PDR001)

Dose level	INC280 Proposed dose	PDR001 Proposed dose *
-1**	100 mg	300 mg
1 (starting dose)	200 mg	300 mg
2***	400 mg	300 mg

*PDR001 will be given at a stable dose (no escalation).

**Dose level -1 represents treatment doses for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study.

***An intermediate dose of INC280 may be explored if needed.

6.2.3 Guidelines for dose escalation and determination of MTD/RP2D

MTD definition

The MTD is defined as the highest combination drug doses expected to cause DLT in less than 33% of the treated patients in the first two cycles of treatment. AEs and laboratory abnormalities considered to be DLTs are defined in Table 6-3.

The applied adaptive Bayesian methodology provides an estimate of the combinations of INC280 and PDR001 not exceeding the MTD. Typically the MTD is a tested combination with maximum probability of targeted toxicity (DLT rate between 16% and <33%). The use of the EWOC principle, i.e., a dose may only be used for newly enrolled patients if the risk of excessive toxicity (DLT rate between 33% and 100%) at the dose is less than 25%, limits the risk that a potential next dose will exceed the MTD (Appendix 3).

Dose cohort modification

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified dose level. The first cohort will be treated with the starting dose of INC280 200 mg BID (p.o.) combined with PDR001 300 mg q3w (i.v.).

Patients must complete a minimum of 2 cycles of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first two cycles of treatment to be considered evaluable for dose escalation decisions (Section 10.1.4). Dose escalation decisions will occur when the cohort of patients has met these criteria. If only 2 patients in a cohort are evaluable and neither patient has experienced a treatment-related toxicity CTCAE grade > 1, dose escalation decisions may be considered.

Dose escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels

[redacted]

evaluated in the ongoing study including safety information, DLTs, all CTCAE grade ≥ 2 toxicity data during cycles 1 and 2, and available PK, and available PD data from evaluable patients. The recommended dose for the next cohort of patients will be guided by the BLRM with EWOC principle.

Bayesian logistic regression model of DLT rate

The adaptive Bayesian methodology provides an estimate of DLT rate for all dose levels of INC280 combined with PDR001 that do not exceed the MTD and incorporates all DLT information from all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval [16-33%) and will always satisfy the EWOC principle. In all cases, the dose for the next cohort will not exceed a 100% increase of INC280 from the previous dose. Smaller increases in dose may be recommended by the Investigators and Novartis upon consideration of all of the available clinical data. Any dose escalation decisions made by Investigators and Novartis personnel will not exceed the dose level recommended by the BLRM using the EWOC principle. If needed to better define the dose-toxicity relationship additional patients may be enrolled to the current dose level, to a preceding dose level, or to an intermediate dose level before proceeding with further dose escalation.

If two patients in a previously untested dose level experience a DLT, enrollment to that cohort will stop, the BLRM will be updated and the next cohort will be opened at the next lower dose level or an intermediate dose level that satisfies the EWOC principle. However, if two patients in a new cohort at a previously tested dose level experience a DLT (e.g., a total of eight patients are treated on this dose level with two DLTs observed), further enrollment to that cohort will stop, the BLRM will be updated with this new information and re-evaluation of the available safety and PK data will occur. By incorporating information gained at the preceding dose cohorts, additional patients may be enrolled into the current dose cohort only if the combination still meets the EWOC principle and as agreed by Investigators and Novartis personnel. Alternatively, if recruitment to the same cohort may not resume, a new cohort of patients may be recruited to a lower dose level as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk for this lower dose level to exceed the MTD remains below 25% (EWOC). Re-escalation may then occur if data in subsequent cohorts supports this (EWOC principle is satisfied) and Investigators and Novartis personnel agree.

Dose escalation will continue until identification of the MTD or a suitable lower dose for the phase II part.

The MTD is identified when the following 3 conditions are met:

a. at least 6 patients have been treated at this dose
b. this dose satisfies one of the following conditions:
    - the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
    - minimum of 12 patients have already been treated on the trial to identify the MTD. Recommendation of RP2D may be made with fewer patients, prior to identification of MTD, or

[redacted]

- significant activity is seen early in the phase Ib part, in which case a recommended dose for expansion may be identified and the phase II groups may be initiated without determination of the MTD.

c. it is the maximum dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference see Section 6.2.3.1.

Multiple dose levels may be evaluated in simultaneous cohorts, as long as none exceeds the maximum dose permitted by the BLRM, and a maximum of 6 patients are treated at a dose level greater than the highest dose previously shown to be safe.

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the first two cycles of treatment, then the BLRM will be updated with this new information before any additional patients are enrolled at that higher dose level. Patients ongoing will continue treatment at their assigned dose levels.

6.2.3.1 Implementation of Dose Escalation Decisions

To implement dose escalation decisions, the available toxicity information (including AEs and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK and PD information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the Investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

6.2.3.2 Intra-Patient dose escalation

Intra-patient dose escalation is not permitted at any time within the first 2 cycles of treatment. After cycle 2 has been completed, individual patients may be considered for treatment at a dose of INC280 higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of INC280, he or she must have tolerated the lower dose for at least 2 cycles of therapy (i.e. he or she must not have experienced any INC280-related toxicity CTCAE grade ≥ 2 at the lower dose originally assigned). Moreover, the new, higher dose with which the patient is to be treated must be a dose that has completed evaluation and has not exceeded the MTD/RP2D. Consultation and agreement with Novartis must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the DAR eCRF page. Data from the first two cycles of treatment at the new dose level will not be formally included in the statistical model describing the relationship between dose and occurrence of DLT. However, these data will be incorporated into the clinical assessment of safety within a dose escalation teleconference.

6.2.4 Definitions of dose limiting toxicities (DLTs)

A DLT is defined as an AE or abnormal laboratory value of CTCAE grade ≥ 3 (assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications) that occurs within the first two cycles of treatment with INC280 in combination with PDR001 during the dose escalation part of the study, with the exceptions described in Table 6-3.

[redacted]

National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 4.03 will be used for all grading. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

The Investigator must notify Novartis immediately of any unexpected CTCAE grade ≥ 3 AEs or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 AEs will be reviewed for all patients at the current dose level.

Table 6-3 Criteria for defining dose limiting toxicities (DLTs) (INC280 combined with PDR001)

DLTs include any AE of CTCAE grade 3 or higher occurring in cycle 1 and/or 2, during the dose escalation part of the study, for which relationship to study treatment cannot be ruled out, with the following exceptions:	
Hematology	Neutropenia CTCAE grade 3 (for > 7 consecutive days) and CTCAE grade 4
	Thrombocytopenia CTCAE grade 3 with clinically significant bleeding
	Thrombocytopenia CTCAE grade 3 (for > 7 consecutive days) Thrombocytopenia CTCAE grade 4
	Anemia CTCAE grade 4
	Lymphopenia CTCAE grade 4
Hepatic	For patients with normal bilirubin baseline: Isolated* total bilirubin CTCAE grade 2 for > 7 consecutive days is a DLT, except for patients with Gilbert's syndrome, for whom isolated total bilirubin is a DLT if CTCAE grade 3 for > 7 days.
	For patients with baseline bilirubin out of normal range: blood bilirubin increased to > 1.5 times above baseline
	For patients with normal baseline AST and ALT and bilirubin value:
	AST or ALT > 5.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis***
	OR
	For patients with abnormal baseline AST or ALT or bilirubin value:
	[AST or ALT > 3 x baseline AND > 5.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined** with [total bilirubin > 2 x baseline] without evidence of cholestasis
Cardiac	Grade ≥ 3 or cardiac event that is symptomatic or requires medical intervention
	Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Grade ≥ 3 Troponin
	QTc interval prolonged Grade ≥ 3 (QTcF ≥ 501 ms) on at least two separate ECGs for > 7 consecutive days
Gastrointestinal	Nausea and vomiting: • Recurrence of CTCAE grade 2 (despite standard anti-emetics) • CTCAE grade ≥ 3 despite standard anti-emetics • CTCAE grade 4
	Diarrhea: • Recurrence of CTCAE grade 2 (despite anti-diarrheal treatment) • CTCAE grade ≥ 3 despite maximal anti-diarrheal treatment • CTCAE grade 4
Hypertension	CTCAE grade 3 hypertension if it persists > 7 days despite treatment
	Grade 4 hypertension
Pneumonitis	CTCAE grade 2 pneumonitis if it persists > 7 days despite treatment with corticosteroids.

[redacted]

DLTs include any AE of CTCAE grade 3 or higher occurring in cycle 1 and/or 2, during the dose escalation part of the study, for which relationship to study treatment cannot be ruled out, with the following exceptions:	
	CTCAE Grade 3-4 pneumonitis of any duration.
Infection	CTCAE grade 3 infection or fever in the absence of neutropenia if they persist > 5 days. CTCAE Grade 4 infection of any duration is a DLT.
Electrolytes	CTCAE grade 3 electrolyte abnormalities if they persist > 7 days despite treatment or are clinically significant. Grade 4 electrolyte abnormality of any duration is a DLT.
Pancreas	Asymptomatic CTCAE grade ≥ 3 serum amylase or lipase (> 2.0 × ULN) occurring for > 7 consecutive days is a DLT Symptomatic serum amylase or lipase elevation, medical intervention required is a DLT
Fatigue/Asthenia	Fatigue/Asthenia CTCAE grade ≥ 3 and lasting > 7 consecutive days is a DLT
Immune-related toxicities	CTCAE grade 3 immune related toxicities if they persist > 7 days despite treatment with corticosteroids Immune related toxicities CTCAE grade 4 of any duration are DLTs.
Other AEs	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in cycles 1 and 2, may be considered to be DLTs by the Investigators and Novartis, even if not CTCAE grade 3 or higher.
*"Isolated total bilirubin" increase defined as: total bilirubin increase without ALT or AST increase; "isolated AST or ALT" increase defined as: AST or ALT increase without total bilirubin increase **"Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold ***"Cholestasis" defined as: ALP elevation [>2xULN 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)	

6.3 Dose modifications

6.3.1 Dose modifications and dose delay for INC280

Dose reductions and modifications for INC280 are described in Table 6-5.

Patients who missed more than 28 consecutive days of INC280 dosing should be discontinued from the study treatment and enter the Safety Follow-up period. In exceptional situations, if the patient is clearly benefiting from the study treatment (i.e. stable disease, partial response, complete response), and in the opinion of the Investigator no safety concerns are present, after documented discussion with Novartis, the patient may remain on study treatment.

Patients who discontinue treatment due to INC280 related toxicities may continue treatment with PDR001 single agent after documented discussion with Novartis.

6.3.2 Dose modifications and dose delay for PDR001

There will be no dose modifications allowed for PDR001.

[redacted]

If a patient experiences an AE meeting the criteria for DLT as outlined in Section 6.2.4 (including events occurring after cycle 2), treatment should be withheld. The same applies for any grade 3 immune related AE (irAE) that would require the use of systemic steroids. Patients can only resume treatment if they are on a prednisone dose of ≤10 mg/day (or equivalent dose if another steroid is used). Following resolution of the toxicity to grade 1 or to the patient's baseline value, the patient may resume study treatment, if there is no evidence of disease progression as per irRC. A decision to resume treatment with PDR001 following the occurrence of a DLT or any grade 3 irAE is at the discretion of the Investigator. If the Investigator considers it to be in the patient's best interest to resume therapy before the toxicity has resolved to grade 1, this may be permitted on a case by case basis, following discussion with Novartis. In case the infusion cannot be administered at the scheduled visit, it has to be administered as soon as possible, and the start of the cycle will be shifted accordingly.

Patients who missed 2 infusions should be discontinued from the study treatment and enter the Safety Follow-up period. In exceptional situations, if the patient is clearly benefiting from the study treatment (i.e. stable disease, partial response, complete response), and in the opinion of the Investigator no safety concerns are present, after discussion with Novartis, the patient may remain on the study treatment

Patients who discontinue the study for an AE or clinically significant abnormal laboratory value must be followed as described in Section 6.3.2. Patients who discontinue treatment due to PDR001 related toxicities may continue treatment with INC280 single agent after documented discussion with Novartis.

All changes in study drug administration must be recorded on the DAR eCRF page.

6.3.3 Follow-up for toxicities related to PDR001

The emergence of irAE may be anticipated based on general experience in clinical studies with similar class of compounds that block the negative immune regulators.

An irAE is a clinically important AE of unknown etiology associated with the study drug exposure. irAEs are typically low grade and self-limited, often occurring after multiple doses, and most frequently involving the GI tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies). Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator, to verify the immune related nature of the AE, and exclude the neoplastic, infectious or metabolic origin of the AE. Management Algorithms (Appendix 4) have been developed to assist Investigators in assessing and managing the following groups of AEs: Gastrointestinal; Renal; Pulmonary; Endocrinopathy; and Skin.

For all the patients whose treatment is interrupted or permanently discontinued due to an irAE, AE 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 30 days, and subsequently at approximately 30-day intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

In case of a suspected irAE, the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed. In case of a toxicity suspected to be a cytokine release syndrome, the assessments outlined in Section 7.2.2.5.6 must be performed. All patients must

[redacted]

be followed-up for irAEs, AEs and SAEs for 150 days following the last dose of PDR001 and 30 days following the last dose of INC280 (in case PDR001 was discontinued >120 days before). Table 6-4 and Appendix 4 outline the follow-up evaluations recommended for selected toxicities.

Table 6-4 Follow-up evaluations for selected toxicities related to PDR001

TOXICITY	FOLLOW-UP EVALUATION
Infusion Reaction	
Grade 1	Infusion interruption not indicated; intervention not indicated.
Grade 2	Stop infusion immediately, and keep line open. Provide supplemental oxygen and fluids, as needed. Monitor vital signs (e.g., blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution. Administer medications for symptomatic relief as needed: - **Urticaria**: Diphenhydramine (25 to 100 mg i.v.) as needed every 4 to 6 hours, or alternative as appropriate. - **Fever**: Acetaminophen/paracetamol (650-1000 mg by mouth) as needed every 4 to 6 hours, or alternative as appropriate. - **Rigors**: Meperidine 25 mg i.v. as needed every 6 hours or alternative as appropriate. Corticosteroids may be administered, as needed. **Resume infusion** once infusion reaction resolves **(within 8 hours of initial start of infusion):** Maintain dose level. Administer oral pre-medication (e.g.1000 mg of acetaminophen/paracetamol, 50-100 mg diphenhydramine hydrochloride or alternative antihistamine), within 60 minutes of restarting the infusion. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then discontinue patient from PDR001.
Grades 3 and 4	Discontinue infusion immediately, and discontinue patient from study. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (e.g., blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.
Pneumonitis	Management Algorithms (Appendix 4)
Renal AE- Creatinine increase	Management Algorithms (Appendix 4)
Skin AE- Rash	Management Algorithms (Appendix 4)
Endocrinopathy- TSH	Management Algorithms (Appendix 4)
GI AE Diarrhea/Colitis	Management Algorithms (Appendix 4)

[redacted]

TOXICITY	FOLLOW-UP EVALUATION
Other immune related toxicities	
Grade 1	Monitor closely until resolution and treat symptoms as appropriate.
Grade 2	Hold study drug and treat with corticosteroids (up to 10 mg prednisone or equivalent per day) and other supportive care as clinically indicated until resolution to grade 1.
Grades 3 and 4	Permanently discontinue study drug. Treat with high dose corticosteroids (≥ 40 mg prednisone or equivalent per day) and other supportive care as clinically indicated.
Cytokine Release Syndrome (CRS)	
Grades 2, 3 and 4	If CRS is suspected (very high fever and precipitous drops in blood pressure) treat with corticosteroids. Take blood for cytokine measurements immediately after the occurrence of the AE and during treatment. If very high levels of IL-6 can be confirmed, a more specific treatment may be used.

6.3.3.1 Dose modifications and dose delay for INC280 and PDR001

Table 6-5 Dose reduction and interruption criteria

Worst toxicity CTCAE Grade[a] (value)	Recommended dose modifications any time during a cycle of therapy, including intended day of dosing
HEMATOLOGIC	
Neutrophil count decreased (ANC) Neutropenia	
Grade 1 and 2 (< LLN - 1000/mm^3, < LLN – 1.0 x 10^9/L)	Maintain dose level of INC280 and continue PDR001 dosing.
Grade 3 (< 1000 - 500/mm^3; < 1.0 – 0.5 x 10^9/L)	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 2, then: If resolved ≤ 7 days, resume INC280 treatment at same dose level and resume PDR001 dosing. If resolved > 7 days, resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing*.
Grade 4 (< 500/mm^3; < 0.5 x 10^9/L)	Omit INC280 dose/delay PDR001 dosing until resolved to ≤ grade 2, then resume INC280 treatment ↓ 1 dose level and resume PDR001 dosing*.
Febrile neutropenia (ANC < 1000/mm^3 (< 1.0 x 10^9/L), fever > 38.3°C (101 °F)	Omit dose/delay PDR001 dosing, then: If resolved in ≤ 7 days, resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing*. If resolved in > 7 days, discontinue INC280 treatment and consider resuming PDR001 dosing alone*.
Platelet count decreased (Thrombocytopenia)	
Grade 1 or 2 (< LLN – 50 x 10^9/L)	Maintain dose level of INC280 and continue PDR001 dosing.
Grade 3 (< 50 – 25 x 10^9/L) without clinically significant bleeding	Maintain dose level of INC280 and continue PDR001 dosing. If resolved ≤ 7 days, continue INC280 treatment at same dose level and continue PDR001 dosing*. If resolved > 7 days, continue INC280 treatment at ↓ 1 dose level and continue PDR001 dosing.

Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
Grade 3 (< 50 – 25 x 10^9/L) with clinically significant bleeding	Omit dose until resolved to grade ≤ 2, then: If resolved ≤ 7 days, resume INC280 treatment at same dose level and resume PDR001 dosing*. If resolved > 7 days, resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing.
Grade 4 (< 25 x 10^9/L)	Omit dose until resolved to grade ≤ 2, then resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing***. If toxicity recurs, discontinue patient from INC280 treatment and consider resuming PDR001 dosing alone*.
RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level of INC280 and PDR001
Grade 2 (> 1.5 - 3.0 x ULN) Grade 3 (> 3.0 – 6.0 x ULN)	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1 or baseline, then: If resolved in ≤ 7 days: Resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing. If resolved in > 7 days, permanently discontinue patient from INC280 and PDR001 treatment.
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from INC280 and PDR001 treatment.
HEPATIC	
Isolated total bilirubin elevation - For patient's whose baseline total bilirubin is ≤ ULN	
>ULN – 2.0 x ULN	Maintain dose level of INC280 and continue PDR001 dosing with liver function tests (LFTs) monitored.
>2.0 – 3.0 x ULN	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1, then If resolved in ≤ 7 days, resume treatment at the same dose level and resume PDR001 dosing. If resolved in > 7 days, resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing.
Grade 3 (> 3.0 - 10.0 x ULN) [d]	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1, then If resolved in ≤ 7 days, resume treatment at ↓ 1 dose level and resume PDR001 dosing*. If resolved in > 7 days, discontinue patient from INC280 treatment and consider resuming PDR001 dosing alone*.
Grade 4 (> 10.0 x ULN) [c]	Permanently discontinue patient from INC280 treatment and delay PDR001 dosing until resolved to grade ≤ 1, then consider resuming PDR001 dosing alone*.
Isolated total bilirubin elevation - For patient's whose baseline total bilirubin is > ULN[c]	
>ULN – 2.0 times above baseline	Maintain dose level of INC280 and continue PDR001 dosing with LFTs monitored.
>2.0 – 3.0 times above baseline	Omit INC280 dose/delay PDR001 dosing until resolved to baseline, then If ≤ 7 days, resume treatment at the same dose level and resume PDR001 dosing. If > 7 days, resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing.

[redacted]

Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
>3.0 times above baseline	Omit INC280 dose/delay PDR001 dosing until resolved to baseline, then If ≤ 7 days, resume treatment at ↓ 1 dose level and resume PDR001 dosing*. If > 7 days, discontinue patient from INC280 treatment and consider resuming PDR001 dosing alone*.
Grade 4 (> 10.0 x ULN) [c]	Permanently discontinue patient from INC280 treatment and delay PDR001 dosing until resolved to grade ≤ 1, and consider resuming PDR001dosing alone*.
Isolated AST or ALT elevation for patient's baseline AST/ALT are ≤ ULN	
Grade 1 and 2 (> ULN - 5.0 x ULN)	Maintain dose level of INC280 and continue PDR001 dosing.
Grade 3 (> 5.0 – 20.0 x ULN)	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1, then If resolved in ≤ 7 days, resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing. If resolved in > 7 days, discontinue INC280 permanently and continue with PDR001 alone.
Grade 4 (>20.0 x ULN)	Discontinue INC280 permanently. Once resolved to grade ≤ 1, consider resuming PDR001 dosing alone*.
Isolated AST or ALT elevation for patient's baseline AST/ALT are > ULN	
> ULN - 3.0 times above baseline	Maintain dose level of INC280 and continue PDR001 dosing.
> 3.0 – 5.0 times above baseline but <5.0 x ULN	Maintain dose level of INC280 and continue PDR001 dosing.
> 3.0 – 5.0 times above baseline but >5.0 x ULN	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1/back to baseline, then If resolved in ≤ 7 days, resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing. If resolved in > 7 days, discontinue INC280 permanently and continue with PDR001 dosing alone.
5.0 times above baseline	Discontinue INC280 permanently. Once resolved to grade ≤ 1 or baseline, consider resuming PDR001 dosing alone*.
Combined [b e] elevations of AST or ALT and total bilirubin For patients with normal baseline ALT or AST or total bilirubin value: 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 [AST or ALT>2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [total bilirubin >2x baseline] AND >2.0 x ULN without evidence of cholestasis [d]	Discontinue INC280 permanently in the absence of signs of cholestasis, hemolysis, and alternative causes of the liver injury have been excluded (e.g., concomitant use of hepatotoxic drug(s), alcoholic hepatitis, etc.). Once resolved to grade ≤ 1 or baseline, consider resuming PDR001 dosing alone*.

Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
METABOLIC	
Asymptomatic amylase and/or lipase elevation (If symptomatic elevations of any grade, discontinue INC280 permanently)	
Grade 1 and 2 (> ULN - 2.0 x ULN)	Maintain dose level of INC280 and continue PDR001 dosing.
Grade 3 (> 2.0 - 5.0 x ULN)	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 2, then If resolved in ≤ 14 days, resume treatment at same dose level and resume PDR001 dosing. If resolved in > 14 days, resume treatment at ↓ 1 dose level and resume PDR001 dosing.
Grade 4 (> 5.0 x ULN)	Permanently discontinue patient from INC280 treatment. Once resolved to grade ≤ 1 or baseline, consider resuming PDR001 dosing alone*.
CARDIAC	
Myocarditis or other cardiac event	
Recommended clinical management of myocarditis grade ≥ 2 or other cardiac event grade ≥ 3: Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg QD and consult with a cardiologist (hospitalization as indicated)	
Grade 1	Maintain dose level of INC280 and continue PDR001 dosing
Myocarditis grade ≥ 2	Permanently discontinue IN280 and PDR001
Other cardiac event grade ≥ 3	Permanently discontinue IN280 and PDR001
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 and 2 (QTcF 450-500 ms)	Maintain dose level of INC280 and continue PDR001 dosing
Grade 3 (QTcF ≥ 501 ms on at least two separate ECGs)	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 2, then: If resolved ≤ 7 days, resume treatment at the same dose level and resume PDR001 dosing. If resolved > 7 days, resume treatment at ↓ 1 dose level and resume PDR001 dosing.
Grade 4 (QTcF ≥ 501 ms or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue patient from INC280 treatment. Once resolved to grade ≤ 1 or baseline, consider resuming PDR001 dosing alone*.
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
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 ILD/pneumonitis to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage. For the follow-up and management of ILD like events/pneumonitis, also refer to Appendix 4, Pulmonary Adverse Event Management Algorithm.	
Grade 1	Interrupt INC280 during diagnostic workup for ILD/Pneumonitis; consider delay of PDR001 dosing. 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.

[redacted]

Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
	If it recurs after resumption of study drug permanently discontinue INC280.
Grade 2	Mandatory: Interrupt INC280 and delay PDR001 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 INC280. Only in the absence of a diagnosis of ILD/Pneumonitis, study drug may be restarted following these guidelines: • If resolves to ≤ Grade 1 in ≤ 7 days reduce INC280 by 1 dose level. • If fails to resolve to ≤ Grade 1 within 7 days or recur after resumption of study drug at decreased dose, permanently discontinue INC280.
Grade 3 and Grade 4	Mandatory: Permanently discontinue study drugs. Treat with IV steroids as clinically indicated. Oxygen therapy as indicated.
GASTROINTESTINAL	
Pancreatitis	
Grade 2	Maintain dose level of INC280 and continue PDR001 dosing.
Grade ≥ 3	Permanently discontinue patient from INC280 treatment. Once resolved to grade ≤ 1 or baseline, resume PDR001 dosing alone*.
Diarrhea **	
Grade 1 (despite maximal anti-diarrheal medication)	Maintain dose level of INC280 and continue PDR001 dosing.
Grade 2 (despite maximal anti-diarrheal medication)	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1, then resume INC280 treatment/PDR001 dosing at same dose level. If diarrhea returns as grade ≥ 2, omit INC280/delay PDR001 dosing dose until resolved grade ≤ 1, then resume INC280 treatment ↓ 1 dose level. Continue PDR001 dosing*.
Grade 3 or 4 (despite maximal anti-diarrheal medication)	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1, then resume INC280 treatment at ↓ 1 dose level and discontinue PDR001 dosing*.
Vomiting	
Grade 1 (despite standard anti-emetics)	Maintain dose level of INC280 and continue PDR001 dosing.
Grade 2 (despite standard anti-emetics)	Omit INC280 dose until resolved to grade ≤ 1, then resume treatment at same dose level. If vomiting returns as grade ≥ 2, omit INC280 dose until resolved to grade ≤ 1, then resume INC280 treatment at ↓ 1 dose level and continue PDR001 dosing*.
Grade 3 and 4 (despite standard anti-emetics)	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1, then resume INC280 treatment at ↓ 1 dose level and discontinue PDR001 dosing*.
Nausea	
Grade 1 or 2 (despite standard anti-emetics)	Maintain dose level of INC280 and continue PDR001 dosing.

[redacted]

Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
Grade 3 (despite standard anti-emetics)	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1, then resume INC280 treatment at ↓ 1 dose level and consider resuming PDR001 dosing*.
SKIN AND SUBCUNTANEOUS TISSUE DISORDERS	
Rash/photosensitivity * **	
Grade 1 or 2	Maintain dose level of INC280 and continue PDR001 dosing.
Grade 3, despite skin toxicity therapy	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing. If resolved in > 7 days (despite appropriate skin toxicity therapy), discontinue patient from INC280 treatment and consider resuming PDR001 dosing alone*.
Grade 4, despite skin toxicity therapy	Discontinue patient from INC280 treatment. Once resolved to grade ≤ 1 or baseline, consider resuming PDR001 dosing alone*.
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue PDR001 and INC280 treatment.
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue/Asthenia	
Grade 1 or 2	Maintain dose level of INC280 and continue PDR001 dosing.
Grade 3	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, resume INC280 treatment at same dose level and resume PDR001 dosing. If resolved in > 7 days, resume INC280 treatment at ↓ 1 dose level and resume PDR001 dosing.
Grade 4	Discontinue patient from INC280 treatment. Once resolved to grade ≤ 1 or baseline, consider resuming PDR001 dosing alone*.
Peripheral edema	
Grade 1 or 2	Maintain dose level of INC280 and continue PDR001 dosing
Grade 3	Omit INC280 dose until resolved to grade ≤ 1, then resume INC280 treatment at ↓ 1 dose level; continue PDR001 dosing
Grade 4	Discontinue patient from INC280 treatment and delay PDR001. Once resolved to grade ≤ 1 or baseline, consider resuming PDR001 dosing alone*.
Other adverse events	
Grade 1 or 2	Maintain dose level of INC280 and continue PDR001 dosing, consider initiating appropriate support medication. For any intolerable grade 2 (e.g. limiting instrumental ADL), consider omitting the dose until resolved to grade ≤ 1, then ↓ 1 dose level.
Grade 3	Omit INC280 dose/delay PDR001 dosing until resolved to grade ≤ 2, then resume INC280 treatment ↓ 1 dose level and resume PDR001 dosing.
Grade 4	Discontinue patient from INC280 treatment. Once resolved to grade ≤ 1 or baseline, consider resuming PDR001 dosing alone*.

[redacted]

Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03) [b] 'Combined' defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold. [c] Note: 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. [d] 'Cholestasis' defined as: ALP elevation (> 2 x ULN and R value (ALT/ALP in x ULN) < 2) in patients without bone metastases, or elevation of ALP liver fraction in patients with bone metastases [e] If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for 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, re-start treatment either at the same dose or one dose lower if meeting a criterion for dose reduction. *If the Investigator considers it to be at the patient's best interest to resume therapy before the toxicity has resolved to Grade 1, this may be permitted on a case by case basis, following discussion with Novartis. **Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea. ***During the whole duration of treatment with INC280, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing and avoid sunbathing or using a solarium extensively). 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.	

Table 6-6 Follow-up hepatic toxicities

TOXICITY	FOLLOW-UP EVALUATION
HEPATIC Isolated total bilirubin elevation Isolated AST/ALT elevation	**Total bilirubin CTCAE Grade 1**: Monitor (liver function tests) LFTs per protocol or more frequently if clinically indicated **Total bilirubin CTCAE Grade 2**: Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN **Total bilirubin 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 **Total bilirubin 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 weeks **AST/ALT CTCAE Grade 2 elevation:** 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 **AST/ALT CTCAE Grade 3 elevation:** For AST/ALT 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 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 **AST/ALT CTCAE Grade 4 elevation:** 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.
Combined AST or ALT and total bilirubin elevation	**Combined elevations of AST or ALT and total bilirubin**: After discontinuing the patient from INC280 permanently, repeat LFTs as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)
*Note: this table refers only to the evaluation schedule to monitor selected toxicities. Refer to Table 6-5 for dose modifications required for applicable toxicities	

[redacted]

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

Patients with transaminase increase combined with 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 values; 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≤2), hepatocellular (R≥5), or mixed (R>2 and <5) liver injury.

In the absence of cholestasis, these patients should be immediately discontinued from INC280 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, 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, if PK analysis is performed in the study.
- 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.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus meeting the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

[redacted]

6.4 Anticipated risks and safety concerns of the study drug

6.4.1 PDR001

Appropriate eligibility criteria and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, i.e. infusion reaction, pneumonitis, are provided in Section 6.3.2 and Appendix 4. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

6.4.2 INC280

Based upon the clinical experience with INC280, the overall risk-benefit assessment of INC280 is considered favorable. Most of the AEs that have been reported, irrespective of relationship to study drug, have been manageable and generally mild or moderate in severity. Hepatic toxicity events and liver function test alterations (ALT and/or AST increase) have been observed in a number of patients. Appropriate eligibility criteria as well as specific dose modification and stopping rules and toxicity follow-up criteria have been included in this protocol. For more details refer to clinical toxicity data provided in the [INC280 Investigator's Brochure]. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

6.4.3 INC280 combined with PDR001

This is the first time INC280 in combination with PDR001 will be tested in humans.

PDR001 is a monoclonal antibody, and is not metabolized by cytochrome P450 (CYP450) enzymes, or transported by P-gylcoprotein (P-gp) or related ABC membrane transporters. The clinical relevance of cytokines impacting the levels of P-gp and CYP450 with administration of PDR001 is unknown but considered unlikely. INC280 is moderately metabolized by cytochrome P450 (CYP) 3A4 *in vitro*, with an expected contribution by aldehyde oxidase.

Pharmacokinetic drug-drug interaction (DDI) is expected to be low between INC280 and PDR001.

6.5 Concomitant medications

6.5.1 Permitted concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed.

- Antivirus medications to manage HBV or HCV infection and/or prevent reactivation (e.g. tenofovir); supportive care.
- Medications to prevent or treat nausea or vomiting.
- Anti-diarrheal medications (e.g., loperamide) for patients who develop diarrhea.
- Pain medication to allow the patient to be as comfortable as possible.
- Localized radiotherapy and treatment with bisphosphonates for pre-existing, painful bone/liver metastases is permitted (non-target lesions).

[redacted]

- Nutritional support or appetite stimulants (e.g. megestrol).
- Oxygen therapy and blood products or transfusions.

The patient must be told to notify the investigational site about any new medications, herbal remedies and dietary supplements he/she takes after the start of the study treatment. All medications (other than study treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered within 21 days prior to the first administration of study treatment through 30 days after the last administration of INC280/150 days after the last administration of PDR001 must be listed on the Prior and Concomitant Medications or the Surgical and Medical Procedures eCRF. Prior antineoplastic therapies including medications, radiotherapy, and surgery are to be recorded on the separate Prior Antineoplastic Therapy eCRF page during screening.

6.5.2 Permitted concomitant therapy requiring caution and/or action

Treatment with hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) may not be initiated during the study. If a patient is using erythroid stimulating agents (ESAs) prior to enrollment (at least 2 weeks before start of study treatment), they may continue at the same dose.

Anticoagulation is permitted if the patients are already at stable doses of warfarin or stable doses of low molecular weight heparin (LMWH) for >2 weeks at time of first dose and INR should be monitored as clinically indicated per Investigator's discretion. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor biopsy according to the institutional guidelines.

Anti-hypertensives are allowed as concomitant medications; however, because transient hypotension has occurred during infusions of monoclonal antibodies, consideration should be given to withholding anti-hypertensive medications for 12 hours prior to infusion with PDR001.

INC280 is a moderate CYP1A2 inhibitor. Co-administration of INC280 increased sensitive CYP1A2 probe substrate (caffeine) AUC by 135% (see Section 1.2.1.2). 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 concomitant drug for dose adjustment.

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.

Co-administration of INC280 with a strong CYP3A4 inhibitor (itraconazole) increased INC280 AUC by 40%. There is no change in INC280 Cmax. Execute caution when use 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.

[redacted]

Short acting gastric acid modulators containing aluminum hydroxide and magnesium hydroxide, or calcium carbonate can be taken. However, it is recommended to take these drugs at least 3 hours before or 3 hours after administration of INC280.

H2 receptor antagonists should be used with caution. If patients are using H2 receptor antagonists during the course of this study, patients should not take INC280 within 2 hours of taking H2 receptor antagonists. In addition, the next scheduled dose of INC280 should be administered at least 8 hours after taking H2 receptor antagonists.

Co-administration of INC280 increased exposure of P-gp substrate and BCRP substrate. Monitor patients closely for symptoms of increased exposure to P-gp or BCRP substrates. Consult the concomitant P-gp or BCRP substrate product information when considering dose adjustment.

Drugs with known risk of causing Torsades de Pointes (TdP) should be avoided. If such drugs cannot be avoided, patients should be more closely monitored by ECG, according to local practice. For identification of drugs with known risk of TdP please refer to qtdrugs.org and Appendix 6 for a list of drugs with known risk of TdP.

6.5.3 Prohibited concomitant therapy

During the course of the study, patients must not receive other additional investigational drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication may be administered while on this study.

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed while patients are receiving study drugs, with the exception of:

- replacement-dose steroids (defined as 10mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids) such as in the setting of adrenal insufficiency,
- prophylactic use for patients with contrast dye allergies, given as per local guidelines or practice,
- the treatment of transient exacerbation of chronic inflammatory conditions such as COPD. In cases where patients are not discontinued from study drugs, steroids must be reduced to 10mg/day (or lower dose) of prednisone or equivalent dose of corticosteroids, prior to the next treatment with PDR001,
- the treatment of PDR-related irAEs or PDR001 infusion reaction. In cases where patients are not discontinued from study drugs, steroids must be reduced to no more than 10mg/day of prednisone or equivalent dose of corticosteroids, prior to the next treatment with PDR001.

Topical, inhaled, nasal and ophthalmic steroids are not prohibited.

The use of live vaccines is not allowed through the whole duration of the study. Inactivated vaccines are allowed.

Co-administration of INC280 with a strong CYP3A4 inducer (rifampicin) decreased INC280 AUC by 66% and Cmax by 56%. Strong inducers of CYP3A4 should be discontinued 7 days

[redacted]

prior to the start of INC280 treatment and are prohibited during the course of the study as decreased INC280 exposure may lead to reduced efficacy.

Therapeutics or supplements with herbal-origination for the purpose of hepatic protection or supportive care of liver diseases, which are particularly considered as common practices in Asia, are also prohibited during the study treatment.

6.6 Patient numbering, treatment assignment or randomization

6.6.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.) that is assigned when the patient is enrolled for screening/baseline. The Patient No. is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by NIRT 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 Patient No. available to the Investigator through the NIRT interface. Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition eCRF page.

6.6.2 Treatment assignment or randomization

The assignment of a patient to a particular cohort during phase Ib and the assignment of a patient into one of the two treatment groups (INC280 in combination with PDR001 or PDR001 single agent) during the phase II part will be coordinated a Novartis Interactive Response Technology (NIRT) system.

Randomization Phase II part

Once the patient has signed the ICF, the Investigator or his/her delegate will log on to the NIRT and register the patient. Prior to dosing he/she or delegate will log on to the NIRT again (at the cycle 1 day 1 visit) to confirm that the patient fulfills all screening inclusion/exclusion criteria and that the patient can initiate study treatment. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition eCRF page. NIRT must be updated within 2 days if the patient will not start treatment.

Prior to dosing, all patients in the phase II part of the study, who fulfill all inclusion/exclusion criteria will be randomized via NIRT to one of the treatment arms (Section 4.1 and Section 6.1) in a ratio of 1:1. Randomization will be stratified by region (Asian versus non-Asian patients).

The NIRT system will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be administered to the patient.

[redacted]

6.7 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 by authorized site personnel only. All dosages prescribed to the patient, all dose changes and interruptions during the study must be recorded on the Dosage Administration Record eCRF page.

Study treatment INC280 and PDR001, will be provided as global clinical supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

INC280

INC280 tablets (in bottles) including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled visit.

PDR001

PDR001 will be administered intravenously as a 30 minute infusion (up to 2 hours, if clinically indicated). Further instructions for the preparation and dispensation of PDR001 are described in the [INC280X2108 Pharmacy Manual].

6.7.1 Study drug packaging and labeling

PDR001 100 mg powder for solution for infusion will be supplied by Novartis to Investigators as open label bulk medication.

The INC280 packaging has a 2-part 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.

6.7.2 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, INC280 and PDR001 should be stored according to the instructions specified on the drug labels and in the current Investigator's Brochures.

6.7.3 Study drug compliance and accountability

6.7.3.1 Study drug compliance

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.

[redacted]

Study treatment will be administered to the patient by the study site staff. Compliance will be assured by administration of the study treatment under the supervision of Investigator or his/her designee.

6.7.3.2 Study drug accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment according to local institutional drug accountability processes. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

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.

6.7.4 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 7-2 list all of the assessments and indicate 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 eCRF will be used as a source document.

Screening evaluations must be performed ≤ 21 days of Cycle 1 Day 1 except for the pregnancy test which is to be performed within 3 days prior to the first dose of study treatment. Assessments performed as part of the screening evaluations and within 3 days prior to the first dose of study treatment, are not required to be repeated on the first dosing day. Laboratory and radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within the screening time window (for Phase Ib and II). The time window for tumor biopsies may be longer than 21 days.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of +/- 3 days is allowed (with the exception of the 150 days safety follow-up visit and survival follow-up contact, for which a visit window of +/- 7 days is allowed). If the infusion of PDR001 is delayed, the start of the next cycle will be shifted accordingly. On PK collection days the windows are provided in Section 7.2.3.2.

Radiological assessments must be performed +/- 7 days of the scheduled date of the assessment.

[redacted]

Table 7-1 Visit evaluation schedule

			Screening Phase	Treatment Phase																	Follow-Up	
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**							**Cycle 2**		**Cycle 3**							**Subsequent cycles**	**End of treatment**	**Safety F/U[6]**	**Disease Progression F/U**	**Survival F/U**
Day of cycle			-21 to -1	1	2	3	4	8	11	15	1	15	1	2	3	4	8	11	15					
Obtain Informed Consent	D	7.1.1	X																					
Demography	D	7.1.1.2	X																					
Inclusion/ exclusion criteria	D	5.2 and 5.3	X																					
Medical History	D	7.1.1.2	X																					
Diagnosis and extent of cancer	D	7.1.1.2	X																					
Prior antineoplastic therapy	D	7.1.1.2	X																					
Prior/concomitant medications	D	7.1.1.2	X	Continuous until the 30 day safety follow-up[6]																				
Physical examination	S	7.2.2.1	X	X				X		X	X	X	X							X	X			
Height	D	7.2.2.3	X																					
Weight	D	7.2.2.3	X	X							X		X							X	X			
Vital signs	D	7.2.2.2	X	X				X		X	X	X	X							X	X			
Performance status	D	7.2.2.4	X								X		X							X	X			
Child Pugh status	D	7.2.2	X	To be assessed every 12 weeks after baseline																	X			

[redacted]

			Screening Phase	Treatment Phase																	Follow-Up	
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**							**Cycle 2**		**Cycle 3**							**Subsequent cycles**	**End of treatment**	**Safety F/U[6]**	**Disease Progression F/U**	**Survival F/U**
Day of cycle			-21 to -1	1	2	3	4	8	11	15	1	15	1	2	3	4	8	11	15					
Hematology	D	7.2.2.5.1	X	X				X		X	X	X	X							X	X			
Chemistry	D	7.2.2.5.2	X	X				X		X	X	X	X							X	X			
Hepatitis markers	D	7.2.2.5.8	X								X		X							X	X			
HIV	D	7.2.2.5.8	X																					
Coagulation	D	7.2.2.5.3	X																					
Urinalysis	D	7.2.2.5.4	X	If clinically indicated																				
Thyroid function	D	7.2.2.5.5	X	X							X		X							X	X			
Hepatotoxicity tests	D	6.3.3.2		If clinically indicated																				
Cytokines (IFN-γ; IL-6) for safety	D	7.2.2.5.6	X	In case of a suspected cytokine release syndrome																				
Pregnancy test in serum	D	7.2.2.5.9	X								X		X							X	X			
Pregnancy test in urine	S	7.2.2.5.9																				X	X	
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5																				X[6]	X	X

[redacted]

			Screening Phase	Treatment Phase																	Follow-Up	
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**							**Cycle 2**		**Cycle 3**							**Subsequent cycles**	**End of treatment**	**Safety F/U[6]**	**Disease Progression F/U**	**Survival F/U**
Day of cycle			-21 to -1	1	2	3	4	8	11	15	1	15	1	2	3	4	8	11	15					
Tumor evaluation (CT/MRI) as per RECIST 1.1 and as per irRC.		7.2.1	X	Every 2 cycles from Cycle 3 Day 1 up to Cycle 11 Day 1, then every 3 cycles until progression of disease per irRC or patient withdrawal. For disease progression f/u, every 6 weeks until 42 weeks, then every 12 weeks until progression of disease per irRC, withdrawal of consent or lost to follow-up. EOT: If a scan was not conducted within 30 days prior to end of study treatment.																		
Alpha Fetoprotein	D	7.2.2.5.7	X	Alpha Fetoprotein to be done coincidentally with tumor scan – Phase II only																				
ECG	D	7.2.2.6.1	X	X							X		X							X	X			
Adverse events	D	8		Continuous																				
Collection of newly obtained tumor sample	D	7.2.4	X	X[2]																				
Collection of newly obtained tumor sample at progression	D	7.2.4		Optional sample collected upon disease progression, for patients who had a response to treatment (as determined by the investigator).																				
Study Drug administration	D	6.1.1		PDR001 i.v. every 3 weeks; INC280 p.o BID																				
PK sampling INC280 Phase Ib and II	D	7.2.3.2		X							X		X							X[3]				
PK sampling PDR001 Phase Ib	D	7.2.3.3		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X[3]	X			
PK sampling PDR001 Phase II	D	7.2.3.3		X	X			X		X	X		X	X			X		X	X[3]	X			

[redacted]

			Screening Phase	Treatment Phase																	Follow-Up	
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**							**Cycle 2**		**Cycle 3**							**Subsequent cycles**	**End of treatment**	**Safety F/U[6]**	**Disease Progression F/U**	**Survival F/U**
Day of cycle			-21 to -1	1	2	3	4	8	11	15	1	15	1	2	3	4	8	11	15					
[redacted]																								
Survival contact	D	7.1.5																						X

[redacted]

[2] Anytime from 6-9 weeks after Cycle 1 Day 1 and at disease progression for patients who had a response (optional).

[3] Cycles 4-6 only and at disease progression.

[4] Every 12 weeks (cycle 7, 11, 15 etc.)

[redacted]

[6] Safety evaluations for 150 days after the last dose of study treatment with contacts at 30-, 90- and 150-day. After initiation of new antineoplastic therapy, only AEs/SAEs suspected to be related to study treatment will be collected. Pregnancy tests every month until the 150-day safety follow-up; can be performed at home or a local doctor's office if the patient is not coming to the clinic. Concomitant medications collected until the 30-day safety follow-up or the start of new antineoplastic therapy, whichever occurs first.

For Japan only, patients enrolled in Phase I are required to be hospitalized during Cycle 1.

[redacted]

7.1.1 Screening

The study IRC/IEC approved ICF must be signed and dated before any screening procedures are performed, except for laboratory and radiological evaluations performed as part of standard of care.

In the phase Ib and phase II part, cMET will be assessed retrospectively. If a patient is considered eligible with regards to the main inclusion/exclusion criteria, the Investigator or designee should complete the Patient Allocation Form and send it to Novartis (Phase Ib only).

The tumor samples can be submitted for analysis as formalin fixed tumor sample or FFPE block prepared from multiple passes (3-6) of a core needle tumor biopsy. For details of sample quality requirements refer to the [INC280X2108 Laboratory Manual]. For details refer to Section 7.2.4.

The allocation of patients to treatment in phase II (INC280 in combination with PDR001 or PDR001 single agent) will be done by NIRT.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 7-1 and Table 7-2. Screening assessments must be repeated if performed outside of the specified screening window (Section 7.1).

7.1.1.1 Information to be collected on screening failures

A patient who signed the ICF but failed to be started on treatment for any reason will be considered a screen failure. The screening failure reason will be entered on the Screening Phase Disposition eCRF Page.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. Molecular results will be collected and reported for all patients, including screen failures. No other data will be entered into the clinical database for those patients, unless the patient experienced a SAE during screening (see Section 8 for SAE reporting details).

7.1.1.2 Patient demographics and other screening/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, prior medication, procedures, significant non-drug therapies, Hepatitis B and C status and any other assessments that are done for the purpose of determining eligibility for inclusion in the study.

7.1.2 Treatment period

A treatment cycle is defined as 21 days for the purposes of scheduling procedures and evaluations. Please refer to Table 7-1 for details of the timing of required assessments and Section 7.1 for visit windows.

Patients will be treated until they experience unacceptable toxicity, progressive disease per irRC and/or treatment is discontinued at the discretion of the Investigator or the patient, as described in Section 7.1.5 and Section 4.3. Patients should not discontinue treatment based on progressive

[redacted]

disease per RECIST v1.1, unless the Investigator confirms that the patient is not benefiting from treatment.

Patients who have disease progression and have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue treatment with INC280 combined with PDR001 or PDR001 single agent. In addition, PDR001/INC280 treatment may be temporarily interrupted to permit local therapy for symptomatic metastases. Patients who continue on treatment after disease progression should discontinue study treatment once they are no longer deriving benefit as assessed by the Investigator.

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. An End of Treatment Phase Disposition CRF page should be completed, giving the date and reason for stopping the study treatment.

7.1.3 Discontinuation of Study Treatment

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 eCRF page. 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.

Study treatment may be discontinued under the following circumstances:

- Adverse event
- Lost to follow-up
- Physician's decision
- Progressive disease per irRC (not per RECIST)
- Study terminated by Novartis
- Subject/guardian decision
- Protocol deviation

Patients must be withdrawn if any of the following occur:

- Death
- Pregnancy

Patients who discontinue study treatment should undergo as soon as possible and within 14 days of the last dose of study drug or within 14 days of the decision to discontinue study treatment, an End of study Treatment (EOT) visit and then be discontinued from the study (please refer to Table 7-1 and Table 7-2 for list of assessments to be performed). If the decision to discontinue the patient occurs at a regular 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 eCRF page should be completed, giving the date and reason for stopping the study treatment. End of

[redacted]

treatment/Premature withdrawal visit is not considered as the end of the study. The Investigator must also register the patient's discontinuation from study treatment in NIRT.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.1.5. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone calls, e-mail, letter) should be made to contact them as specified in Section 7.1.6. If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the Post Treatment Disposition eCRF page.

Patients who transfer to another clinical study or an alternative treatment option to continue provision of study treatment will perform the end of treatment procedures.

7.1.3.1 Replacement policy

Phase Ib dose escalation part:

Patients will not be replaced on study. However, if a patient is considered to be non-evaluable for the Dose Determining Set (DDS), enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients. Enrollment of new patients may be considered until at least the minimum number or at most the maximum number of evaluable patients is achieved within the cohort. Minimum and maximum numbers of evaluable patients per cohort are defined in Section 6.2.3.

Phase II part:

During the phase II part no replacements will be needed.

7.1.4 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 anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the subject'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 subject are not allowed unless safety findings require communicating 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.

[redacted]

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject'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.

Lost to follow-up: For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

7.1.5 Follow-up period

All patients must have safety evaluations for 150 days after the last dose of PDR001 and 30 days after the last dose of INC280 (in case PDR001 has been discontinued > 120 days before). The evaluations can be done either by telephone call or visit. During the 150-day safety follow-up for PDR001, the patient should be contacted for the 30-, 90- and 150-day safety follow-up. Concomitant medications will be collected until the 30-day safety follow-up has been completed or the start of a new antineoplastic therapy, whichever occurs first. Data collected should be added to the Adverse Events eCRF pages, the antineoplastic therapies since discontinuation of study treatment eCRF page and the Concomitant Medications eCRF page. For female patients of child bearing potential, a pregnancy test will be performed at the time points listed in Table 7-1.

Patients who discontinue study treatment for any reason other than death, disease progression per irRC, lost to follow-up, consent withdrawal, start of new anti-cancer therapy or study termination, should also return for tumor evaluation assessments (disease progression follow-up: every 6 weeks until week 42, then every 12 weeks until progression of disease per irRC or lost to follow-up) and should not be considered withdrawn from the study until 80% of the patients enrolled in the phase II part have completed survival follow-up period (minimum 18 months after the first dose of treatment) or discontinued the study for any reason. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient had disease progression.

Upon completion of the 150-day/30-day safety follow-ups (noted above) or disease progression follow-up, patients will be followed for survival every 3 months +/- 1 week (can be done by telephone call) until death or until the end of the study is reached, unless they withdraw consent or are lost to follow-up.

Antineoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

For patients who transfer to another clinical study or an alternative treatment option to continue provision of study treatment, as described in Section 4.3, 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, e-mail, letters). 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 eCRF page.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be assessed locally according to the two following criteria:

1. RECIST v1.1 (based on Appendix 1, Eisenhauer et al 2009).
2. irRC (Appendix 2, based on Wolchok et al 2009 and Nishino et al 2013).

During the course of the study, Novartis may decide to have a central review of the radiological assessments performed. In such case, the Investigator's staff will be instructed on how to send data from these radiological assessments to a Contract Research Organization (CRO) for central review when needed.

Patients will not be withdrawn from the study due to progressive disease per RECIST v1.1, unless the Investigator confirms that the patient is not benefiting from treatment. Please refer to Appendix 1 and Appendix 2 for further details.

The imaging assessment plan is presented in Table 7-2.

Table 7-2 Disease assessment plan

Procedure	Screening	During Treatment/Follow-up
CT or MRI with contrast enhancement (Chest, Abdomen, Pelvis)	Mandated	**During treatment** starting on Cycle 3 Day 1, every 2 cycles until cycle 11 day 1, and then every 3 cycles until progression of disease per irRC or patient withdrawal. **Follow-up for progression**: Every 6 weeks until week 42, then every 12 weeks until progression of disease per irRC or lost to follow-up. **EOT**: If a scan was not conducted within 30 days prior to end of study treatment.
Brain CT or MRI with contrast	If brain metastases are suspected	If disease was detected at baseline, or if clinically indicated

[redacted]

Screening assessments

Imaging assessments will be performed at screening within 21 days of start of treatment (Day -21 to Day -1 prior to Cycle 1 Day 1).

Any imaging assessments already completed during the regular work-up of the patient within 21 days prior to start of treatment, including before signing the study ICF, can be considered as the screening images for this study. Any imaging assessments obtained after randomization cannot be considered screening images. The assessments required at screening are indicated in Table 7-2.

If a patient is known to have a contraindication to CT intravenous (i.v.) contrast media or develops a contraindication during the study, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

If brain metastases are suspected at screening, brain MRI or CT should be completed. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

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.

Chest X-rays and ultrasound should not be used to measure tumor lesions.

Post-screening imaging assessments

Imaging assessments as described in Table 7-2 should be performed using the same imaging modality used at screening, irrespective of study treatment interruption or actual dosing. Imaging assessments for response evaluation will be performed every 6 weeks (+/- 7 days) after screening.

Additional imaging assessments may be performed at any time during the study at the Investigator's discretion to support the efficacy evaluations for a patient, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at screening must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of i.v. contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST v1.1 (Appendix 1).

[redacted]

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, body height and weight, performance status, hematology, chemistry, coagulation, hepatitis markers, Child Pugh status, thyroid function, pregnancy, ECG, as well as collecting of the (S)AEs at every visit. For details on SAE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

Physical examination will be performed according to Table 7-1.

At Screening and Cycle 1 Day 1, prior to PDR001 infusion and/or INC280 intake, a complete physical examination will be performed and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

From Cycle 1 Day 8 onwards, a short physical examination will be performed. A short physical exam will include the examination of general appearance, vital signs (blood pressure [BP] and pulse) and body sites as directed by symptoms.

Significant findings that were present prior to the signature of the study ICF must be included in the Medical History eCRF page. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event eCRF page.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before dosing and as indicated in Table 7-1 as per institutional standards. Vital signs should be assessed in the same position throughout the study.

More frequent examinations may be performed at the discretion of the Investigator if medically indicated, and will be recorded as unscheduled assessment.

7.2.2.3 Height and weight

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

7.2.2.4 Performance status

ECOG performance status will be assessed according to Table 7-3 and as indicated in Table 7-1.

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

[redacted]

Grade	ECOG Status
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Note: Grade 5 (death) was removed from this table. This information will be collected on a separate eCRF.	

7.2.2.5 Laboratory evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally. Refer to Table 7-4 for a summary of the parameters to be evaluated according to Table 7-1. Samples for these parameters will be collected prior to the dosing of study medication.

More frequent evaluations may be performed at the Investigator's discretion if medically indicated; results should be recorded as unscheduled laboratory assessments.

Novartis will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. 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 from that laboratory.

Table 7-4 Local/Central clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Sodium, Potassium, Creatinine, Glucose, Serum amylase, Serum lipase, Creatinine clearance Magnesium, Inorganic Phosphate, Total Bilirubin (also measure direct and indirect bilirubin if total bilirubin is grade > 1), Blood Urea Nitrogen (BUN) or Urea
Tests for hepatotoxicity follow-up (if clinically indicated)	LFTs: albumin, ALT, AST, GGT, total bilirubin, direct and indirect bilirubin, ALP, ALP fractionated (quantification of isoforms – if feasible at study sites) Refer to Section 6.3.3.2 for laboratory tests required in case of potential DILI cases
Coagulation	Prothrombin time (PT), Prothrombin time (quick test) or International normalized ratio [INR]), activated partial thromboplastin time (APTT)
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific Gravity, White Blood Cells)
Hepatitis markers	HBV-DNA, HBsAg, HBcAb, HBsAb, HCV RNA-PCR
Virology	HIV
Thyroid	Free T4, TSH
Cytokines*	Gamma-Interferon (γ-IFN), Interleukin-6 (IL-6)
Tumor marker	Alpha Fetoprotein (AFP)
Pregnancy	Serum and/or urine samples only for women of childbearing potential
*Will be done centrally.	

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.

[redacted]

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.

It should be noted in the patient's eCRF if the patient was fasting at the time of blood sampling.

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.

7.2.2.5.4 Urinalysis

Abnormal findings will be followed up with a microscopic evaluation and/or additional assessments as clinically indicated. A microscopic evaluation (WBC/HPF, RBC/HPF, and any other evaluations depending on macroscopic findings) need only to be performed if the urinalysis result is significantly abnormal.

Urinalysis will be performed at screening and if clinically indicated.

7.2.2.5.5 Thyroid function

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

7.2.2.5.6 Cytokine analysis

Samples for the cytokine panel outlined in Table 7-4 will be collected at the following time points:

- Screening/Baseline
- On an ad-hoc basis in case a patient has an adverse event suspected to be a cytokine release syndrome (Table 7-1). In such case, this assessment should be performed at the following time points:
  a. within 5 hours (or as soon as possible) after the occurrence of the adverse event,
  b. one week after the occurrence of the adverse event.

Samples for cytokine panel at screening will be stored below -70°C. The samples will be analyzed retrospectively in batches. The analysis of the samples will be done only for patients who experienced an adverse event suspected to be a cytokine release syndrome and had follow-up samples collected.

7.2.2.5.7 Tumor marker

During phase II, alpha fetoprotein (AFP) must be done at screening and matched with the tumor efficacy evaluation. Refer to Table 7-2 for timepoints.

7.2.2.5.8 Virology

During the screening period, patients must be screened for HIV, HBV and HCV (current or past history of infection). Careful medical history must be taken for all patients to look for risk

factors (family history of HBV and HCV, intravenous drug abuse, unprotected sex, dialysis, blood transfusions, etc.), and any past or present HBV symptoms (e.g., jaundice, dark urine, light colored stools, right upper quadrant pain).

Hepatitis B:

At screening, all patients will be tested for:

- HBV-DNA level
- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core antibody (HBcAb)
- Hepatitis B surface antibody (HBsAb)

Monitoring for HBV‑DNA level on day 1 of every cycle and EOT is required for:

- Patients known to have a history of HBV infection, despite a negative viral load test at screening (including patients who were treated and are considered 'cured')
- Patients positive for viral load on HBV-DNA test at screening
- Patients positive for any of the serology at screening

Hepatitis C:

At screening, all patients will be tested for quantitative HCV RNA-PCR.

Monitoring for HCV RNA-PCR level on day 1 of every cycle and EOT is required for:

- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including patients who were treated and are considered 'cured')
- Patients positive for viral load on HCV RNA-PCR test at screening

Virology panel and HIV testing outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.9 Pregnancy and assessments of fertility

All females of childbearing potential will have a serum pregnancy test at screening/baseline and/or within ≤ 72 hours before first dose of study treatment. During the study, a serum pregnancy test should be done at day 1 of each cycle, and at EOT visit.

A urine or serum pregnancy test should be performed every month during and at the end of the safety follow-up period. If the patient is not coming to the clinic during the safety follow-up, it can be performed at home or at a local doctor's office, and the results will be communicated to the site staff. These follow-up pregnancy tests will be recorded only in the source documentation, not in the CRF.

In case of positive urine pregnancy testing- additional testing must be performed to confirm pregnancy and if confirmed follow reporting requirements as described in Section 8.3.

A positive pregnancy test requires immediate discontinuation of study treatment and discontinuation from study.

[redacted]

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 (Table 7-1 and Table 7-5). Blood samples scheduled at the same time point should be taken after the ECGs are completed.

Triplicate ECGs will be done at all timepoints. A PK sample should be collected right after every ECG performed.

Table 7-5 12 lead ECG collection plan

Cycle	Day	Time
Screening	-21 to -1	Anytime
1	1	Pre-dose of INC280 treatment
1	1	1h (±5 min) hour post-dose INC280 treatment and prior to PDR001 treatment
1	1	1h (±5 min) hour post PDR001 treatment (end of infusion)
3	1	Pre-dose of INC280 treatment (or PDR001 treatment in phase II single agent arm)
3	1	1h (±5 min) hour post INC280 treatment and prior to PDR001 treatment (not applicable for phase II PDR001 single agent arm)
3	1	1h (±5 min) hour post PDR001 treatment (end of infusion)
2, 4 and afterwards	1	Pre-dose
EOT	-	Anytime
Unscheduled	-	Anytime

Clinically significant abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page. All eligibility and patient management decisions should be made based on the local reading of the ECG.

Triplicate ECGs will be performed at least 5 minutes apart. All ECGs will be independently reviewed by a central ECG laboratory. Instructions for the collection and transmission of ECGs to the independent reviewer will be provided in the [INC280X2108 ECG Manual].

7.2.3 Pharmacokinetics [redacted] assessments

Blood samples will be collected from all patients for the analysis of plasma INC280 and its major metabolite CMN288, and serum PDR001 concentrations, [redacted]. The PK analysis will be performed according to Section 10.5.4.

[redacted]

7.2.3.1 Pharmacokinetic blood collection and handling

The exact date and clock times of drug administration and PK blood draw will be recorded on the appropriate eCRF page. If vomiting occurs within 4 hours following INC280 administration

[redacted]

on the day of post dose PK blood sampling, the clock time of vomiting should be recorded in the DAR PK eCRF page.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Refer to the [INC280X2108 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

If patients experience a DLT, SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained whenever possible. The date and time of the last dose and the time of PK blood draw should be recorded.

7.2.3.2 Pharmacokinetic sampling for INC280

PK blood samples for INC280 and CMN288 as outlined in Table 7-6 and Table 7-7.

Table 7-6 Schedule of blood collection (plasma) for INC280 (BID) PK for patients participating in phase Ib

Cycle	Day	Scheduled time (hours)
1	1	0 hr / pre-C1D1 AM dose [a]
2	1	0 hr / pre-C2D1 AM dose [a]
2	1	0.5 hr (±5 minutes)
2	1	1 hr (±10 minutes)
2	1	2 hr (±15 minutes)
2	1	4 hr (±30 minutes)
2	1	8 hr (±2 hr)
3	1	0 hr / pre-C3D1 AM dose [a]
4	1	0 hr / pre-C4D1 AM dose [a]
5	1	0 hr / pre-C5D1 AM dose [a]
6	1	0 hr / pre-C6D1 AM dose [a]
NA	NA	Unscheduled and at the time of progression (per irRC)
[a] Take samples immediately prior to administration of INC280		

Table 7-7 Schedule of blood collection (plasma) for INC280 (BID) PK for patients participating in phase II

Cycle	Day	Scheduled time (hours)
1	1	0 hr / pre-C1D1 AM dose [a]
2	1	0 hr / pre-C2D1 AM dose [a]
2	1	1 hr (±10 minutes)
2	1	4 hr (±30 minutes)
2	1	8 hr (±2 hr)
3	1	0 hr / pre-C3D1 AM dose [a]
4	1	0 hr / pre-C4D1 AM dose [a]
5	1	0 hr / pre-C5D1 AM dose [a]
6	1	0 hr / pre-C6D1 AM dose [a]
NA	NA	Unscheduled and at the time of progression (per irRC)
[a] Take samples immediately prior to administration of INC280		

[redacted]

7.2.3.3 Pharmacokinetic [redacted] sampling for PDR001

Blood samples for PDR001 [redacted] analysis will be collected as outlined in Table 7-8 and Table 7-9.

If the dosing of Cycle 3 Day 1 is delayed, the PK sampling for the full PK profile should be delayed accordingly to match the scheduled time points for Cycle 3 as outlined in Table 7-8 and Table 7-9. PK [redacted] samples will be collected also at the End of Treatment visit and in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) [redacted]. After the primary clinical study report (CSR) data cut-off date is reached, no additional PK [redacted] samples will be collected for the patients still ongoing on the study.

Table 7-8 Schedule of blood collection (serum) for PDR001 PK [redacted] for patients participating in phase Ib

Cycle	Day	Scheduled Time Point (h)**	Analytes
1	1	0 hr / pre-C1D1 dose [a]	mAb [redacted]
1	1	1 hr (± 5 min) [b]	mAb
1	2	24 hr (± 2h)	mAb
1	3	48 hr (± 8h)	mAb
1	4	72 hr (± 8h)	mAb
1	8	168 hr (± 8h)	mAb
1	11	240 hr (± 24h)	mAb
1	15	336 hr (±24h)	mAb
2	1	504 (±24h) hr / 0 hr pre-C2D1 dose [a]	mAb [redacted]
2	1	1 hr (± 5 min) [b]	mAb
3	1	0 hr / pre-C3D1 dose [a]	mAb [redacted]
3	1	1 hr (± 5 min) [b]	mAb
3	2	24 hr (± 2h)	mAb
3	3	48 hr (± 8h)	mAb
3	4	72 hr (± 8h)	mAb
3	8	168 hr (± 8h)	mAb
3	11	240 hr (± 24h)	mAb
3	15	336 hr (± 24h)	mAb
4	1	504 (±24h) hr / pre-C4D1 dose [a]	mAb [redacted]
5	1	0 hr / pre-C5D1 dose [a]	mAb [redacted]
6	1	0 hr / pre-C6D1 dose [a]	mAb [redacted]
EOT			mAb [redacted]
Unscheduled and at the time of progression (per irRC)			mAb [redacted]
* [redacted] samples are collected together with PK samples.			
**PK samples are collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10 mL of saline.			
[a.] Take samples immediately prior to the administration of PDR001			
[b.] After completion of the infusion.			

[redacted]

Table 7-9 Schedule of blood collection for PDR001 PK [redacted] for patients participating in phase II

Cycle	Day	Scheduled Time Point (h)**	Analytes
1	1	0 hr / pre-C1D1 dose [a]	mAb [redacted]
1	1	1 hr (± 15 min) [b]	mAb
1	2	24 hr (± 2h)	mAb
1	8	168 hr (± 8h)	mAb
1	15	336 hr (±24h)	mAb
2	1	504 (±24h) hr / pre-C2D1 dose [a]	mAb [redacted]
2	1	1 hr (± 5 min) [b]	mAb
3	1	0 hr / pre-C3D1 dose [a]	mAb [redacted]
3	1	1 hr (± 5 min) [b]	mAb
3	2	24 hr (± 2h)	mAb
3	8	168 hr (± 8h)	mAb
3	15	336 hr (± 24h)	mAb
4	1	504 (±24h) hr / pre-C4D1 dose [a]	mAb [redacted]
5	1	0 hr / pre-C5D1 dose [a]	mAb
6	1	0 hr / pre-C6D1 dose [a]	mAb
EOT			mAb
Unscheduled and at the time of progression (per irRC)			mAb
* [redacted] samples are collected together with PK samples.			
**PK samples are collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10 mL of saline.			
a. Take samples immediately prior to the administration of PDR001			
b. After completion of the infusion.			

7.2.3.4 Bioanalytics

Bioanalysis for pharmacokinetic [redacted] assessment will employ the validated assays:

1. The assay to quantify PDR001 will be a validated LCMS. The details of the assay will be documented in the [INC280X2108 Laboratory Manual].
2. The assay to quantify and assess the [redacted] will be a validated homogeneous ELISA. The details of the assay will be documented in the [INC280X2108 Laboratory Manual].
3. INC280 will be measured in plasma by a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay.

[redacted]

7.2.3.5 PK [redacted] sample handling, labeling, and shipping instructions

A total of 3 mL of blood will be collected at specified time points for INC280 and CMN288 analysis, and another 3 mL of blood for PDR001 analysis. For time points when PDR001 (mAb) PK [redacted] are to be measured, [redacted]. **Blood samples should be collected from the arm opposite from the investigational drug infusion, or from another site.** After clotting, the resulting serum will be separated in aliquots and will be stored frozen until analysis. Please see the [INC280X2108 Laboratory Manual] for detailed instructions about collection, handling and shipment of samples.

The actual collection date and time of each sample will be entered on the Pharmacokinetics/[redacted] Blood Collection eCRF pages.

7.2.4 Biomarkers

In this study biomarker analyses will be used to investigate the effect of INC280 in combination with PDR001 and PDR001 single agent at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes. [redacted]

While the goal of the biomarker assessments 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/or analysis may be omitted at the discretion of Novartis.

The sample collection information must be entered on the appropriate sample collection log eCRF and requisition form(s). Detailed instructions for the collection, handling, and shipment of biomarker samples are outlined in the [INC280X2108 Laboratory Manual].

Table 7-10 Biomarker sample collection plan (tumor/blood samples)

Sample Type	Visit/ Time point	Volume	Marker*	Purpose
Tumor samples				
Newly obtained tumor sample	Screening (recommended to be collected at least 2 weeks after the last dose of sorafenib) 6-9 weeks after start of study treatment	Newly obtained formalin fixed tumor sample in ethanol (3-6 passes)	[redacted] Expression by IHC (e.g., CD8, PD-L1, [redacted] [redacted]	[redacted] Pharmacodynamic (PD) markers [redacted]

[redacted]

Sample Type	Visit/ Time point	Volume	Marker*	Purpose
	At progression of disease only for patients who had a response as per investigator assessment (optional)		[redacted]	[redacted]
[redacted]				

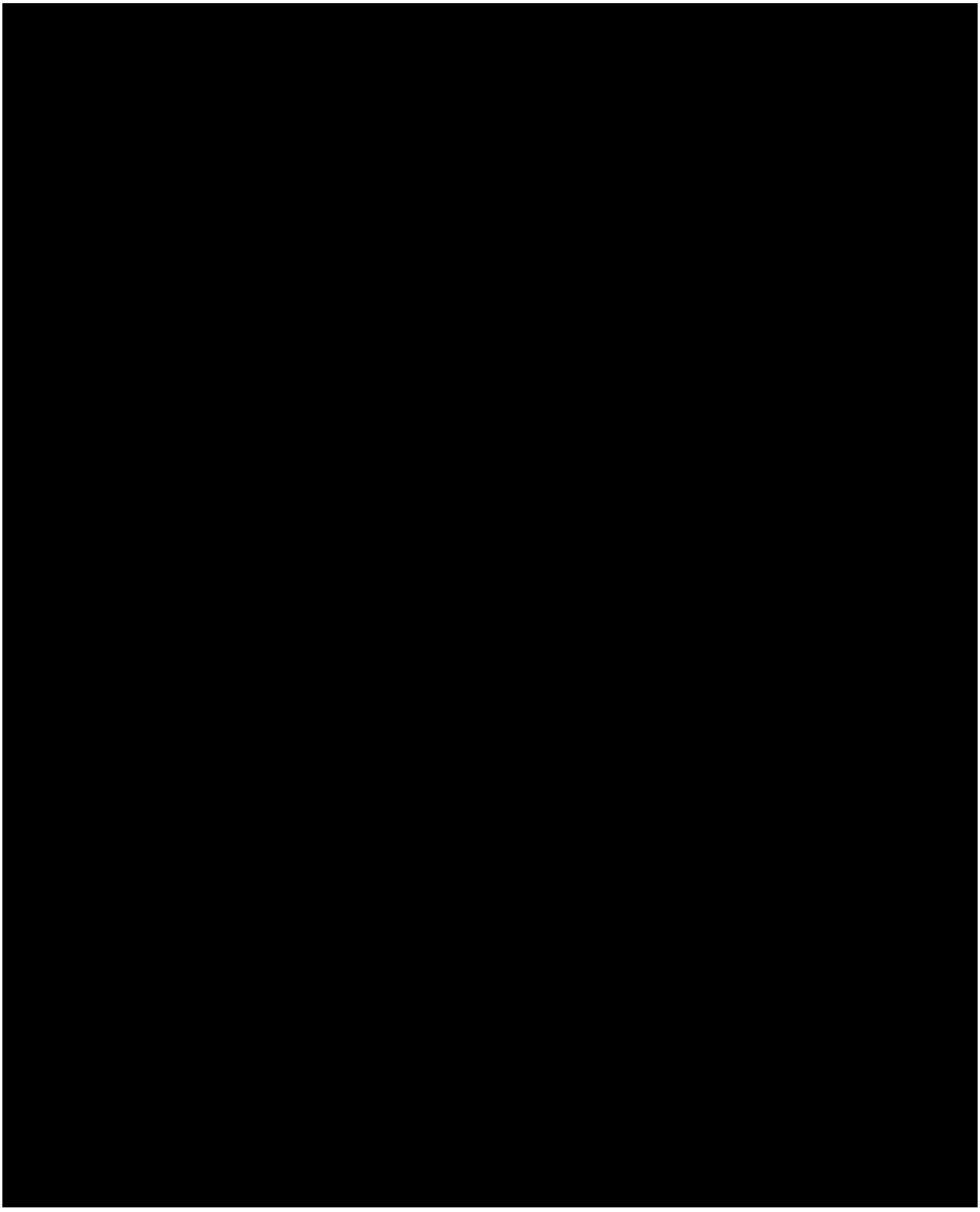
Note: On days and time points when biomarker and pharmacokinetic blood samples are being collected, the PK sample must be drawn first.

7.2.4.1 Tumor Collection

Collection of evaluable paired (e.g. baseline and on-treatment) tumor samples is critical to assess the pharmacodynamic effect on the tumor microenvironment of PDR001 single agent or in combination with INC280 as described in Table 7-10. Submission of evaluable newly obtained tumor samples, at screening and again 6-9 weeks after the start of study treatment, is therefore mandated for all patients in the study. An optional tumor sample is requested to be collected at disease progression, for patients who had a response as per investigator assessment. Exceptions may be made on a case by case basis following a documented discussion with Novartis.

[redacted]

[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. For additional details about irAE, please refer to Section 6.3.2.

Once the 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).

[redacted]

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of INC280 (in case PDR001 was discontinued >120 days before) and 150 days after the last dose of PDR001. After initiation of a new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected in the Adverse Event CRF. 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 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 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:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1, and which seriousness criteria have been met.

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 eCRF.

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 irRC or as per RECIST), 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.

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 eCRF. 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 AE (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per 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

[redacted]

- 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.

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST or irRC. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event.

Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the Investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

8.2.2 Reporting

For patients who sign the ICF, SAE collection will start upon signing the ICF. SAEs will only be reported if the event is suspected to be causally related to study procedure as assessed by the Investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped INC280 (in case PDR001 was discontinued >120 days before) and 150 days after the patient has stopped PDR001, must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up 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.

Any SAEs experienced after this 30 days after the last dose of INC280 (in case PDR001 has been discontinued >120 days before) and 150 days (after the last dose of PDR001) period should only be reported to Novartis if the Investigator suspects a causal relationship to the study treatment. If a patient starts a post treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment will be reported.

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

[redacted]

Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the Investigator folder provided to each 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 INC280 or PDR001 Investigator's Brochures or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis 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 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. After the mother has provided consent, the newborn will be followed-up for 12 months.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis CMO&PS Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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 formal data monitoring board will not be used for this study. This is an open-label, Phase Ib/II study in which patients will receive INC280 in combination with PDR001 or PDR001 single agent. Novartis will have access to the Safety Data on a regular basis. Novartis will host Investigator teleconferences on a regular basis during the study. Further, during the phase I part of the study Novartis and the Investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose escalation teleconference the clinical course (safety information including both DLTs and all CTCAE Grade 2 or higher toxicity data during the first two cycles of treatment, and PK data) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well.

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of patients will be guided by the BLRM with EWOC and a medical review of relevant clinical, PK and laboratory data. Novartis and the Investigator parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or recruit an additional cohort of patients at the current dose level (Section 10.4.2).

During the phase II part of the study 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 that time (Section 10.7).

8.6 Steering Committee

A Steering Committee constituted of members of the Translational Clinical Oncology Leadership Team will be formed for this study. If the monitoring of the study data requires a decision to be taken on the continuation of the study, then the relevant data (e.g., safety data or primary analysis and predictive probability of success) will be communicated to the Steering Committee for decision making purposes.

9 Data collection and management

9.1 Data confidentiality

Information about study patients 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.

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

[redacted]

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 (Patient 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 Patient Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient 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 eCRFs 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 eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, administered, 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 eCRFs 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 eCRF 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 eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated Investigator's 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 have been trained. Automatic validation programs check for data discrepancies in the eCRFs allow modification or verification of the entered data by the Investigator's staff.

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.

[redacted]

PK and biomarker (blood, serum, plasma and/or tissue) samples obtained during the course of the study will be collected from the Investigator sites and analyzed by a Novartis designated laboratory, contracted central laboratories, or local laboratories. ECG data collected during the study will be reviewed and processed centrally by a specialist CRO. During the course of the study, Novartis may decide to have a central review of the radiological assessments performed. In such case, the Investigator's staff will be instructed on how to send data from these radiological assessments to a Contract Research Organization (CRO) for central review when needed. Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Field monitors will review the eCRFs and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the field monitor or by the designated investigational site staff; and one copy will be retained at the investigational site.

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.

Samples and/or data 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

Data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the Investigator must be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. Data will be summarized with respect to demographic and screening characteristics, efficacy and safety observations and measurements and all relevant PK and PD measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

The study data will be analyzed and reported based on all patients' data of the dose escalation and phase II parts up to the time when all patients have potentially completed at least nine cycles of treatment or discontinued the study. Any additional data for patients continuing to receive

[redacted]

study treatment past the data cutoff date for the primary Clinical Study Report (CSR), as allowed by the protocol, will be reported at completion of the study as defined in Section 4.3.

The following rules will be followed for reporting results unless stated otherwise:

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

- For the phase Ib part, cohorts treated with the same combination dose level will be pooled into a single treatment group. All summaries, listings, figures and analyses will be performed by treatment group.
- For the phase II part, all summaries, listings, figures will be presented by study treatment for safety and efficacy analyses, unless otherwise specified.

Study treatments in the phase II part:

- Treatment A: PDR001+INC280
- Treatment B: PDR001

Note: patients from the phase Ib dose escalation parts and the phase II part will not be pooled in any analyses unless otherwise specified.

Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data, Section 7.1.1.1, collected will not be included in analyses, but will be reported in the CSR as separate listings.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of study treatment in the phase Ib part, and all patients to whom study treatment has been assigned by randomization in the phase II part. According to the intent to treat principle, patients in the phase II part will be analyzed according to the treatment they have been assigned to during the randomization procedure.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study treatment. Patients will be classified according to treatment received, where treatment received is defined as:

- the treatment assigned if it was received at least once, or
- the first treatment received when starting therapy with study treatment if the assigned treatment was never received.

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

10.1.3 Per-Protocol Set

The Per Protocol Set (PPS) for the phase II part consists of a subset of FAS patients who meet the following criteria:

- Treatment according to the randomization scheme (see Section 6).

[redacted]

- Presence of at least one measurable lesion at screening according to RECIST v1.1 as per Appendix 1.
- Have not been previously treated with PD-1- or PD-L1-directed therapy or any therapeutic cancer vaccine.

All protocol deviations leading to exclusion from the PPS will be detailed in the RAP. Patients will be classified according to the received treatment.

The PPS will be used in the phase II part of the study only and will define the patients used in the sensitivity analysis of the primary endpoint (see Section 10.4.4). If the PPS and the FAS are identical, then analyses described by the PPS will not be performed.

10.1.4 Dose-determining analysis set (DDS)

Phase Ib part (INC280 in combination with PDR001)

The DDS analysis consists of all patients in the dose escalation part who either meet the minimum exposure criterion and have sufficient safety evaluations, or have experienced a DLT during cycles 1 and 2. This constitutes an evaluable patient for the determination of MTD.

A patient is considered to have met the minimum exposure criterion if having received two planned doses of PDR001 and 28 days of INC280 during cycles 1 and 2. Patients who do not experience a DLT during the first two cycles are considered to have sufficient safety evaluations if they have been observed for ≥ 42 days following the first dose, and are considered by both Novartis and the Investigators to have enough safety data to conclude that a DLT did not occur.

Patients who do not meet these minimum dosing and safety evaluation requirements will be regarded as ineligible for the DDS and additional patients may be enrolled if required to meet the minimum cohort size for decision making, as described in Section 6.2.3.

10.1.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have at least one blood sample providing measurable INC280 and PDR001 PK data. The PAS will be used for all PK analyses.

Note: Some patients' data may not be adequate for the reliable estimation of some PK parameters. These patients will be identified and their PK parameters will be excluded from summaries. The criteria of exclusion will be detailed in the RAP.

10.2 Patient demographics/other baseline characteristics

Demographic and other screening data (including disease characteristics) will be listed and summarized descriptively by treatment group/study treatment on the FAS.

[redacted]

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

For each of INC280 and PDR001, the actual dose and duration in days of treatment as well as the dose intensity (computed as actual dose received/actual duration) and the relative dose intensity (computed as the ratio of dose intensity to planned dose/planned duration) will be listed and summarized by means of descriptive statistics by treatment group/study treatment. Categories for relative dose intensity of INC280 or PDR001 will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented by treatment group/study treatment.

The reason for discontinuation from treatment will be summarized, and listed along with dates of first and last dose of INC280 and PDR001, duration of exposure to INC280 and PDR001 and date of discontinuation for each patient.

10.3.2 Concomitant therapies

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

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. Protocol deviations will be identified prior to database lock and will be listed and summarized by treatment group/study treatment. Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions, see Section 10.5.3.6.

10.4 Primary objective

Phase Ib part

To characterize the safety and tolerability of INC280 in combination with PDR001 and identify the MTD and/or RP2D.

Phase II part

- The primary objective is to compare the anti-tumor effect of INC280 in combination with PDR001 vs. PDR001 single agent.

10.4.1 Variable

Phase Ib part

- Safety: Incidence of dose limiting toxicities (DLTs) in the first two cycles of treatment. Incidence and severity of AEs and SAEs, including changes in laboratory parameters, vital signs and ECGs
- Tolerability: dose interruptions, reductions and dose intensity

[redacted]

Estimation of the MTD will be based upon the BLRM of the probability of a DLT for patients in the DDS.

Phase II part

The primary variable is the Overall Response Rate (ORR), defined as the proportion of patients with a best overall response of CR or PR based on local Investigator assessment, as defined in RECIST v1.1 (Appendix 1).

Estimation of the true ORR in this part of the study will be based upon the observed overall response for patients in FAS, using a Bayesian analysis.

10.4.2 Statistical hypothesis, model, and method of analysis

10.4.2.1 Phase Ib part

For the analysis of safety and tolerability endpoints see Section 10.5.3.

Identification of a recommended dose

Estimation of the MTD of the treatment will be based upon the estimation of the probability of dose limiting toxicity (DLT) in cycles 1 and 2 for patients in the DDS. A recommended dose below the MTD may be identified based on other safety, clinical, PK, and PD data (Section 6.2.3).

Bayesian adaptive approach

The dose escalation will be guided by a Bayesian analysis of DLT data in cycles 1 and 2 for INC280 and PDR001. The Bayesian analysis will be based on a model with three parts, representing:

- Single agent INC280 toxicity
- Single agent PDR001 toxicity
- Interaction

Single agent toxicity is modelled using logistic regression for the probability of a patient experiencing a DLT against log-dose. The odds of a DLT are then calculated under no interaction for the two single agent toxicities, and interaction is accounted for by adjusting these odds with an additional model parameter (odds multiplier). Details of the model are given in Appendix 3.

Assessment of patient risk

After each cohort of patients, the posterior distribution for the risk of DLT for new patients at combination doses of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0 , 0.16)
Targeted toxicity:	[0.16 , 0.33)
Excessive toxicity:	[0.33 , 1]

[redacted]

The escalation with overdose control (EWOC) principle

Dosing decisions are guided by the escalation with overdose control principal (Rogatko 2007). A combination dose may only be used for newly enrolled patients if the risk of excessive toxicity at that combination dose is less than 25%.

Prior distributions

A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent INC280 and PDR001 model parameters. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data (Spiegelhalter et al 2004, Neuenschwander et al 2010, Neuenschwander et al 2014). MAP priors are derived from hierarchical models, which take into account possible differences between the studies.

A full description of the application of the MAP approach to derive the prior distributions of the single agent INC280 and PDR001 model parameters is given in Appendix 3.

The prior distribution for the interaction parameter was based upon prior understanding of possible drug safety interactions. This prior allows for the possibility of either synergistic or antagonistic interaction, and is fully described in Appendix 3.

Starting dose

The starting dose is INC280 200 mg BID and PDR001 300 mg Q3W (Section 6.2.1). For this dose the prior risk of excessive toxicity is 13.9 %, which satisfies the EWOC criterion. A full assessment of the prior risk to patients is given in Appendix 3.

Incorporation of data from ongoing studies

The dose-DLT information generated from the safety patient cohort of INC280 in combination with PD-1 inhibitors in the ongoing study [CEGF816X2201], if available by the time of having dose escalation meetings in this study will be incorporated in the model. A direct down-weighting approach will be used to account for between-trial heterogeneity. Details are provided in Appendix 3.

Listing of DLTs

DLTs will be listed, and their incidence summarized by primary system organ class and worst grade (CTCAE version 4.04). Listings and summaries will be based on the DDS.

10.4.2.2 Phase II part

Patients in each group are randomized in a 1:1 ratio into either PDR001+INC280 arm or PDR001 arm. The randomization is stratified by region: Asian vs. non-Asian. The primary efficacy endpoint ORR will be determined per RECIST v1.1 for the primary analysis.

For the primary analysis, a Bayesian logistic regression model with treatment (combination vs. single agent), region (Asian vs. non-Asian), and interaction of treatment and region as covariates will be applied to provide the inference of ORR. Full details of model

[redacted]

parameterization and prior specification are provided in Appendix 3. The ORRs of the PDR001+INC280 and PDR001 arms will be compared. If the posterior probability that odds ratio (ORR $_{PDR001+INC280}$ to ORR $_{PDR001}$) > 1 is greater than 0.8, AND the observed ORR $_{PDR001+INC280}$ is at least 10% greater than the observed ORR $_{PDR001}$, it will be concluded that the combination treatment has a superior anti-tumor effect compared to the PDR001 single agent treatment.

The posterior mean of ORR adjusted for stratification factor along with 95% credible interval will be provided; the probabilities that the true ORR lies in the following efficacy categories will be reported:

- [0, 20%) no anti-tumor activity
- [20%, 100%] clinically relevant anti-tumor activity

Details of analyses will be provided in RAP.

10.4.3 Handling of missing values/censoring/discontinuations

Patients in the dose escalation part who are ineligible for the DDS will be excluded from the primary analysis, although their data will be used for all remaining analyses.

Patients in the phase II part who have BOR of Unknown (UNK) or not assessed (NA) will be considered as a treatment failure in the primary analysis of ORR. Patients with individual scans of UNK or NA will be handled according to RECIST v1.1 (Appendix 1).

10.4.4 Supportive analyses

For the phase II part, the observed ORR and corresponding 95% exact confidence interval according to Clopper-Pearson method (Clopper and Pearson 1934) will be provided, and by stratum if applicable.

The primary analyses on ORR may be repeated using the PPS.

In addition, ORR will be determined per irRC (Appendix 2) and analyzed with the statistical methods specified for primary analyses using FAS.

[redacted]

Additional analysis may be performed based on cMET status.

10.5 Secondary objectives

Please refer to Table 3-1 for the secondary objectives. The following subsections describe the analyses of related secondary objectives.

10.5.1 Key secondary objective(s)

Not Applicable.

[redacted]

10.5.2 Other secondary efficacy objectives

10.5.2.1 Characterization of efficacy

The BOR, TTP, PFS, DOR, TTR and OS will be analyzed to characterize the efficacy of PDR001 in combination with INC280 and as single agent in the phase Ib part and phase II part. Tumor response related endpoints will be analyzed based on the local Investigator assessments according to RECIST 1.1 and irRC, respectively.

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. BOR, TTP, PFS, DOR, TTR and OS will be listed by patient. The following summaries and analyses will be performed for the phase Ib by treatment group (if at least 10 patients in a treatment group) and for the phase II part by study treatment where applicable:

- BOR will be summarized as observed proportion in each category, and corresponding 90% exact confidence interval (CI). Tumor volume best change from baseline will be presented graphically.
- For TTP, PFS and OS, Kaplan-Meier method will be used to estimate the median and provide the Brookmeyer-Crowley 95% CI along with a graphical presentation as appropriate.
- DOR and TTR will be listed by patient. Summaries of DOR may be provided if a sufficient number of patients responded.

Any additional analyses of the secondary efficacy endpoints will be described in the RAP.

10.5.3 Safety objectives

Incidence and severity of AEs and SAEs, changes in laboratory values, electrocardiograms and vital signs will be used to assess the safety of PDR001 single agent and in combination with INC280.

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group for the phase Ib part, and by study treatment and by study treatment in the phase II part.

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 administration of study treatment
2. on-treatment period: from day of first dose of study medication to 30 days after date of last administration of study treatment
3. post-treatment period: from 31 days after date of last administration of study treatment .

Safety summaries will primarily be based on all data from the on-treatment period. Following last administration of study treatment, adverse events (including serious adverse events), and new antineoplastic therapies are collected for a period of 150 days. Following start of new antineoplastic therapy, only study treatment related adverse events will be collected. Select summaries of related adverse events will be produced for the combined on-treatment and post-treatment periods.

[redacted]

10.5.3.2 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 adverse events (new or worsening from screening) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by treatment group.

Deaths reportable as SAEs, non-fatal serious adverse events and irAEs will be listed by patient and tabulated by type of adverse event and treatment group.

Specific safety event categories (SEC) may be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). SEC will be specified in a case retrieval sheet (CRS) or in the RAP and finalized prior to database lock. For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by 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 categorized by the low/normal/high classifications based on laboratory normal ranges.

If the lower limits of normal ranges used in CTCAE definitions are missing, then they have to be replaced by a clinical meaningful limit.

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

- Frequency table for newly occurring on-treatment Grades 3 or 4.
- 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.

[redacted]

10.5.3.4 Other safety data

Any other safety information collected will be listed and notable values will be flagged. Any statistical tests performed to explore the data will be used only to highlight any interesting

[redacted]

comparisons that may warrant further consideration. Additionally, the following outputs will be produced:

ECG

- Summary of post-baseline notable ECG values.
- Listing of ECG evaluations for patients with at least one abnormality.

Vital signs

Definitions of notably abnormal results will be specified in RAP.

- Shift table baseline to worst on-treatment result.

10.5.3.5 Supportive analyses for secondary objectives

Any supportive analyses that are considered appropriate for secondary variables will be described in the RAP prior to database lock.

10.5.3.6 Tolerability

Tolerability of the study treatment will be assessed by summarizing the number of dose interruptions and reductions. Reasons for dose interruptions and dose reductions will be listed by patient and summarized.

10.5.4 Pharmacokinetics

INC280, CMN288 and PDR001 concentration data will be listed and summarized by treatment group and time point, and listed by treatment group, patient and time point. Descriptive statistics will consist of arithmetic and geometric mean, median, standard deviation, arithmetic coefficient of variation (CV), geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Individual concentration-time profiles as well as mean concentration-time profile will be plotted when applicable.

Where possible, PK parameters will be determined for all patients by applying non-compartmental method(s) using Phoenix WinNonlin version 6.4 or above (Pharsight, Mountain View, CA). Derived PK parameters, including but not limited to those listed in Table 10-1, will be summarized with the descriptive statistics, arithmetic and geometric mean, median, standard deviation, arithmetic CV, geometric CV, minimum and maximum. Only median values and ranges will be given for Tmax. Missing data will not be imputed.

Table 10-1 Noncompartmental pharmacokinetic parameters

AUClast	The area under the curve (AUC) from time zero to the last measurable analyte (INC280, CMN288 or PDR001) concentration sampling time (tlast) (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (mass x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid analyte concentration after study drug administration (mass x volume-1)
Tmax	The time to reach maximum (peak) analyte concentration after study drug dose administration (time)

[redacted]

PAS will be used in all pharmacokinetic data analysis and PK summary statistics, as appropriate.

[redacted]

10.5.4.1 Data handling principles

Missing concentration values will be reported as is in data listings. Concentration values below Lower limit of quantitation (LLOQ) 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]

[redacted]

10.7 Interim analysis

No formal interim analyses are planned.

Phase Ib dose escalation part

The dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose escalation part, the next dose of INC280 in combination with PDR001 has to be chosen depending on the observed data. Details of this procedure and the process for communication with Investigators are provided in Section 6.2.3.

10.8 Sample size calculation

Phase Ib dose escalation part

Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation part including at least six patients at the MTD/RP2D level, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and pharmacokinetic parameters as required. At least 12 patients are expected to be in the dose escalation part. If a recommended phase II dose is identified without determination of the MTD, fewer than 12 patients may be required.

Phase II part

Sample size is considered for assessment of ORR. *A priori* the true mean of ORR is assumed to be 20% in patient groups treated with PDR001 single agent. It is assumed that the combination with INC280 will improve the mean of ORR to 40% . A minimally informative unimodal (Neuenschwander et al 2008) beta prior distribution with mean as assumed is then specified as following:

- PDR001+INC280: $ORR_{PDR001+INC280} \sim Beta(0.67,1)$
- PDR001: $ORR_{PDR001} \sim Beta(0.25,1)$

The ORR of the PDR001 in combination with INC280 treatment will be compared to that of the PDR001 single agent treatment. A Bayesian logistic regression model will be used to perform this comparison. The full model will include a covariate for treatment effect, and will also explore region effects, and treatment/region interaction. Here, operating characteristics are described under the assumption that there is no region effect, and a simplified logistic regression model including only treatment as a covariate is used to provide inference.

[redacted]

Given 30 patients in each treatment, and under the assumption of 20% ORR for PDR001 single agent, the probabilities of success under different assumed scenarios of true ORRs for the combination are presented in Table 10-2.

- For true ORRs for combination and single agent treatment, of 40% and 20%, respectively, the probability to declare superior anti-tumor effect of the combination treatment is 78.5%.
- If the true ORRs of combination and single agent treatment in patients are both 20%, the probability to incorrectly declare superior anti-tumor effect of the combination treatment is 14.1%.

Table 10-2 Operating characteristics for $ORR_{PDR001+INC280}$ vs. ORR_{PDR001} comparison

True ORR_{PDR001}	True $ORR_{PDR001+INC280}$	Probability of success (success when Posterior P(Odds($ORR_{PDR001+INC280}$)/Odds(ORR_{PDR001})>1)>0.80)) & (Observed $ORR_{PDR001+INC280}$ – observed ORR_{PDR001}) > 10%)
20%	10%	0.008
	20%	0.141
	30%	0.433
	40%	0.785
	50%	0.955

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 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.

[redacted]

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 or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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 eCRFs.

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.

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.

11.5 Publication of study protocol and results

Novartis is committed to the 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. ...clinicaltrials.gov, before study start. In addition, results of interventional clinical trials in adult patients are posted on ...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 (...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 presentations 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 ...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 Novartis 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, patients' 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 electronic study case report form (eCRF) is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. Any change or correction to a paper eCRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic eCRFs an audit trail will be maintained by the system. The Investigator should retain records of the changes and corrections to paper eCRFs.

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 Novartis 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 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

14.1 Appendix 1: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

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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

14.1.1 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 14.1.2 and the definition of best response in Section 14.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.3.2 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 14.1.4 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.

14.1.2 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.

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14.1.2.1 Definitions

14.1.2.1.1 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 14.1.3.2.8

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.
- 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.

14.1.2.1.2 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 14.1.3.2.8.

14.1.2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to 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 anti-tumor 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.
- 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.

[redacted]

- 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 tumor samples 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.

14.1.2.3 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

[redacted]

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 eCRF (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 14.1.2.1.1.
- **Nodal target**: See Section 14.1.2.1.1.

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.

14.1.2.4 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 for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

14.1.2.4.1 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.

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.

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.

14.1.2.4.2 Determination of target lesion response

Table 14-1 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]

SOD for CR may not be zero when nodal lesions are part of target lesions

[redacted]

Response Criteria	Evaluation of target lesions
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 Methodology change See Section 14.1.2.2.	

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 eCRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 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 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.

[redacted]

- 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.

14.1.2.4.3 Determination of non-target lesion response

Table 14-2 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

[redacted]

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 14.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.2.4.4 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 eCRF.

- 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 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 14.1.2.5).
- 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 14.1.2.2.

14.1.2.5 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 14-3.

Table 14-3 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]

[redacted]

Target lesions	Non-target lesions	New Lesions	Overall lesion response
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 14.1.2.4.

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.

14.1.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.3.1 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.

[redacted]

- 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).
- 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.

[redacted]

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 overall lesion responses.

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).

14.1.3.2 Time to event variables

14.1.3.2.1 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.

14.1.3.2.2 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").

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.

14.1.3.2.3 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.

14.1.3.2.4 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.

14.1.3.2.5 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.

14.1.3.2.6 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 14.1.3.2.5. 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.

[redacted]

- 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.

14.1.3.2.7 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

[redacted]

is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.3.2.8).

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

14.1.3.2.8 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 14-4.

Table 14-4 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 14.1.2.4.

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.

[redacted]

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.

14.1.3.2.9 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 14.1.3.2.7, 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 14-5 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)

[redacted]

Situation	Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
=Definitions can be found in Section 14.1.3.2.7. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.3.2.7. =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.		
=Definitions can be found in Section 14.1.3.2.7. =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.		

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 14-5 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.

[redacted]

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.

14.1.4 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).

14.1.4.1 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).

14.1.4.2 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 14 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
- Patient/guardian decision
- Death
- Progressive disease per irRC (not per RECIST)
- Study terminated by Novartis

14.1.4.3 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

[redacted]

- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Patient/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by Novartis

14.1.4.4 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 Investigator's 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.

14.1.4.5 Programming rules

The following should be used for programming of efficacy results:

14.1.4.5.1 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.

[redacted]

14.1.4.5.2 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 assessment date is calculated as outlined in Section 14.1.3.2.7). 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.

14.1.4.5.3 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.

14.1.4.5.4 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)'.

14.1.4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

14.1.4.5.6 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 (option
- Death due al, see Table 14-5) to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

[redacted]

*Adequate assessment is defined in Section 14.1.3.2.7. 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 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="Novartis 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.

14.1.5 References (available upon request)

Dent S, Zee B, Dancey J, et al (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791.

Eisenhauer E, Therasse P, Bogaerts J, 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, Carroll KJ, Pemberton K, 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]

14.2 Appendix 2: Guidelines for immune-related Response Criteria (irRC) using one-dimensional measurements (simulating RECIST 1.1)

14.2.1 Introduction

The currently used immune-related response criteria (irRC) uses unidimensional measurements to assess tumor response and it is an adaptation of the original irRC published by Wolchok (Wolchok et al 2009, Nishino et al 2013).

The purpose of this document is to summarize the irRC guidelines in details focusing on differences in tumor response assessments between irRC and RECIST v1.1.

The primary difference between irRC and RECIST 1.1 is the definition of progressive disease. The definitions of baseline target/non target lesions, number of lesions selected at baseline, the criteria for lesion measurement method of evaluation of response and definition of response are the same for irRC and RECIST 1.1 and are available in the RECIST 1.1 guidelines (Appendix 1).

14.2.2 New lesions and non-target lesions

In irRC a new lesion does not automatically indicate progressive disease.

New measurable lesions are added to the sum of diameters of the previously existing target lesions, and the sum of diameters is followed at each subsequent tumor assessment.

New measureable lesions are defined using the same criteria as for baseline target lesions in RECIST v1.1. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions up to 10 lesions in total.

Non-target lesions (baseline and new non-measurable lesions) are used primarily for determination of Complete Response (CR). The RECIST v1.1 definitions for the assessment of non-target lesions apply. A CR requires that all non-target lesions disappear (both those present at baseline and any new non-measurable lesions that have appeared during the study). If after worsening a non-target lesion becomes measurable, it should still be followed as a non-target lesion. Worsening of non-target lesions and new non-measurable lesions only indicate disease progression if there is unequivocal evidence of disease progression (Table 14-6).

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

To assess tumor response, the sum of diameters for all target lesions is calculated (at baseline and throughout the study). The diameters of any new measurable lesions are included in the sum of diameters at each assessment to provide the total tumor burden. At each assessment, percent change in the sum of diameters is calculated and compared to baseline or to nadir in order to evaluate the target lesion response (including new measurable lesions) (Section 14.2.4). This evaluation combined with the status of non-target lesions (baseline and new non-measurable lesions) is then used to determinate the overall lesion response (Table 14-6). The thresholds for irPR and irPD assessment are the same as for RECIST v1.1.

[redacted]

14.2.4 Definitions of response categories and evaluation of overall lesion response

In irRC, the overall response is primarily based on target lesions (baseline and new measurable lesions). The non-target lesions only contribute to define irCR, and irPD in the case of unequivocal progression, as shown below in Table 14-6.

Like in RECIST 1.1, irCR and irPR must be confirmed at a new assessment after at least 4 weeks. Unlike RECIST 1.1, irPD also requires confirmation at a new assessment after at least 4 weeks.

The response categories are defined as follows:

- Immune related Complete Response (irCR): Disappearance of all non-nodal target lesions and non-target lesions in two consecutive observations not less than 4 weeks apart. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. (Sum of diameters may be greater than zero at the time of CR, if nodal lesions are included as target lesions).
- Immune related Partial Response (irPR): At least a 30% decrease in the sum of diameters of all target lesions including new measurable lesions in two consecutive observations not less than 4 weeks apart, taking as reference the baseline sum of diameters.
- Immune related Progressive Disease (irPD): At least a 20% increase in the sum of diameters of all measured target lesions including new measurable lesions. The irPD must be confirmed in a second evaluation not less than 4 weeks later, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Worsening of non-target lesions (existing or new) only indicate PD when there is unequivocal evidence of progression, confirmed in a second evaluation not less than 4 weeks later.
- Immune related Stable Disease (irSD): Neither a sufficient shrinkage to qualify for irPR or irCR, nor an increase in lesions which would qualify for irPD.
- Unknown (UNK): Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a method significantly different from baseline that prevents reasonable comparison to the prior assessments.

Table 14-6 Overall response at each assessment

Target and new measurable lesions (Tumor burden), * (%)	Non-target lesions (both baseline and new non-measurable)	Overall lesion response
- 100	Absent	irCR[a]
- 100	Stable/not evaluated	irPR[a]
≤-30	Absent/Stable/not evaluated	irPR[a]
>-30 and<+20	Absent/Stable/not evaluated	irSD
≥+20	Any	irPD[a]
Any	Unequivocal progression	irPD[a]

*the diameter of new measurable lesions is included in the calculation of the sum of diameters.
[a] To be confirmed after at least 4 weeks.

[redacted]

If the evaluation of any of the target lesions could not be made during follow-up, the overall status must be 'unknown' unless progression was documented.

If the evaluation of any non-target lesions is not made, and all target lesions disappeared, irCR cannot be determined and overall response must be "irPR".

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 irCR.

14.2.5 References (available upon request)

Wolchok JD, Hoos A, O'Day S et al (2009) Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res; 15:7412-20.

Nishino M, Giobbie-Hurder A, Gargano M, et al (2013) Developing a Common Language for Tumor Response to Immunotherapy: Immune-Related Response Criteria Using Unidimensional Measurements. Clin Cancer Res; 19:3936-3943.

[redacted]

14.3 Appendix 3: Statistical details of Bayesian regression models, priors, design operating characteristics and hypothetical dose escalation scenarios

14.3.1 Bayesian logistic regression model specification for dose escalation

This appendix provides details of the statistical model, the derivation of prior distributions from historical data, and the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios.

14.3.1.1 Statistical model

The statistical model comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and an interaction part.

14.3.1.1.1 Single agent parts

Let $\pi^{INC}(d^{INC})$ be the risk of DLT for INC280 given as a single agent at dose d^{INC}; $\pi^{PDR}(d^{PDR})$ be the risk of DLT for PDR001 given as a single agent at dose d^{PDR}. Single agent toxicity is modelled using logistic regression for the risk of DLT against log-dose:

$$\text{INC280:} \quad \text{logit}(\pi^{INC}(d^{INC})) = \log(\alpha^{INC}) + \beta^{INC}\log(d^{INC}/400)$$

$$\text{PDR001:} \quad \text{logit}\left(\pi^{PDR}(d^{PDR})\right) = \log(\alpha^{PDR}) + \beta^{PDR}\log(d^{PDR}/300)$$

where 400mg, 300mg are used to scale the doses of INC280 and PDR001, respectively. Hence, α^{INC} and α^{PDR} (>0) are the single-agent odds of a DLT at 400mg (bid, total daily dose 800mg) and 300mg (q3w), respectively; and β^{INC} and β^{PDR} (>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

The statistical model comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and an interaction part.

14.3.1.1.2 Interaction

Under no interaction, the risk of a DLT at dose d^{INC} of INC280 and dose d^{PDR} of PDR001 is:

$$\pi_0^{comb}(d^{INC}, d^{PDR}) = 1 - \left(1 - \pi^{INC}(d^{INC})\right)\left(1 - \pi^{PDR}(d^{PDR})\right)$$

To allow for interaction between INC280 and PDR001, an odds multiplier is introduced. The risk of DLT for combination dose (d^{INC}, d^{PDR}) is then given by:

$$\text{odds}\left(\pi^{comb}(d^{INC}, d^{PDR})\right) = \exp(\eta \times d^{INC}/400 \times d^{PDR}/300) \times \text{odds}\left(\pi_0^{comb}(d^{INC}, d^{PDR})\right),$$

where $\text{odds}(\pi) = \pi/(1-\pi)$; and η is the log-odds ratio between the interaction and no interaction model at the reference doses. Here $\eta = 0$ corresponds to no interaction, with $\eta > 0$ and $\eta < 0$ representing synergistic and antagonistic toxicity respectively.

[redacted]

14.3.1.2 Prior specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\boldsymbol{\alpha}^{\boldsymbol{INC}})$, $\log(\boldsymbol{\beta}^{\boldsymbol{INC}})$ for INC280, $\log(\boldsymbol{\alpha}^{\boldsymbol{PDR}})$, $\log(\boldsymbol{\beta}^{\boldsymbol{PDR}})$ for PDR001, and the interaction parameter $\boldsymbol{\eta}$. A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters.

14.3.1.2.1 Prior distribution for the logistic parameters

Description of the meta-analytic-predictive (MAP) approach

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical trial s ($s = 1, \ldots, S$). The corresponding probability of a DLT is π_{ds}. The model specifications for the derivation of the MAP prior are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Bin}(\pi_{ds}, n_{ds})$$

$$\text{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log\left(d/d_{ref}\right)$$

$$\left(log(\alpha_s), log(\beta_s)\right) \mid \mu, \psi \sim \text{BVN}(\mu, \psi), \qquad \text{s} = 1, \ldots, S$$

$$\left(log(\alpha^*), log(\beta^*)\right) \mid \mu, \psi \sim \text{BVN}(\mu, \psi)$$

where d_{ref} is the reference dose. The parameters $\mu = (\mu_1, \mu_2)$ and ψ are the mean and between-trial covariance matrix for the logistic parameters, the latter with standard deviations τ_1, τ_2, and correlation ρ. The parameters τ_1 and τ_2 quantify the degree of between trial heterogeneity. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_1 and τ_2, and
- a uniform prior for ρ.

The MAP prior for single-agent model parameters in the new trial, $\left(log(\alpha^*), log(\beta^*)\right)$, is the predictive distribution

$$\left(log(\alpha^*), log(\beta^*)\right) \mid (r_{ds}, n_{ds} : s = 1, \ldots, S)$$

Since the predictive distribution is not available analytically, MCMC is used to simulate values from this distribution. This is implemented using JAGS version 3.4.0. The sample from this distribution is then approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster et al 1977, Wu 1983). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike 1974).

Single agent INC280

For the MAP model for INC280, reference dose $d_{ref} = 400$ mg (bid) is used, and data from $S = 2$ historical studies are available.

[redacted]

Weakly informative normal priors are assumed for μ_1 and μ_2, with means corresponding to an assumed 50% risk of DLT at the reference dose of 400 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to substantial between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander et al 2014).

The prior distributions for the model used for deriving the MAP priors are specified in Table 14-7.

Table 14-7 Prior distributions for the parameters of the MAP model used to derive the prior for the single-agent INC280 model parameters

Parameter	Prior distribution
μ_1	N(mean = logit(1/2), sd = 2)
μ_2	N(mean = 0, sd=1)
τ_1	log-normal(mean = 0.5, sd = log(2)/1.96)
τ_2	log-normal(mean = 0.25, sd = log(2)/1.96)
ρ	uniform(-1,1)

Historical data

The dose-DLT data of INC280 single agent in tablet formulation and BID dosing schedule from the following clinical studies are considered as the relevant information (Table 14-8) and used to derive the prior distribution for the BLRM parameters $\left(log(\alpha^{INC}), log(\beta^{INC})\right)$.

- **CINC280X2102:** a Phase I study on adult patients with cMET dependent advanced solid tumors.
- **CINC280X1101:** a Phase I study of INC280 in Japanese adult patients with advanced solid tumors.

The DLT observation window was 4 weeks in both trials. The AE records of the patients did not show any events that had occurred during the 5th and 6th weeks post-baseline and met the specified DLT criteria.

Table 14-8 Historical dose-DLT data from INC280 single agent clinical studies

Dose in BID (mg)	Number of evaluable patients	Number of DLTs
CINC280X2102		
400	4	0
CINC280X1101		
200	3	0
400	10	1

Single agent PDR001

The prior distribution of PDR001 single agent BLRM model parameters $\left(log(\alpha^{PDR}), log(\beta^{PDR})\right)$ is a mixture of two components: a MAP prior, and a high toxicity prior, which are mixed with weights (0.8, 0.2).

[redacted]

Component 1:

For the MAP model for PDR001, reference dose $d_{ref} = 300$ mg (q3w) is used, and data from $S = 1$ historical studies is available.

Weakly informative normal priors are assumed for μ_1 and μ_2, with means corresponding to an assumed 50% risk of DLT at the reference dose of 300 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to large between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander et al 2014).

The prior distributions for the model used for deriving the MAP priors are specified in Table 14-9.

Table 14-9 Prior distributions for the parameters of the MAP model used to derive the prior for the single-agent PDR001 model parameters

Parameter	Prior distribution
μ_1	N(mean = logit(1/2), sd = 2)
μ_2	N(mean = 0, sd=1)
τ_1	log-normal(mean = 1, sd = log(2)/1.96)
τ_2	log-normal(mean = 0.5, sd = log(2)/1.96)
ρ	uniform(-1,1)

Historical data

The dose-DLT data of PDR001 single agent from the following clinical study are considered as the relevant information (Table 14-9) and used to derive the prior distribution for the BLRM parameters $\left(log(\alpha^{PDR}), log(\beta^{PDR})\right)$.

- **CPDR001X2101:** open label multicenter Phase I/II study of the safety and efficacy of PDR001 administered to patients with advanced malignancies.

The DLT observation window in the Phase I dose escalation part of this trial was 4 weeks. The 6-week AE records of the patients did not show difference from the 4-week data in DLT observation. It is assumed that DLT rate is associated with total exposure of PDR00l within the observation window, and the average weight of a patient is 80 kg. Then each dose level in the historical data d_{qKw}[mg/kg] (K = 2 or 4) can be converted to a flat dose level in a q3w dosing schedule, d_{q3w} [mg], using the following method:

$$d_{q3w}\ [mg] = d_{qKw}[mg/kg] * 80[kg] / K[week] * 3[week].$$

[redacted]

Table 14-10 Historical dose-DLT data from PDR001 single agent clinical studies

Dosing schedule	Dose level (mg/kg)	Converted to dose level in q3w (mg)	Number of evaluable patients	Number of DLTs
q2w	1	120	16	0
q2w	3	360	15	0
q2w	10	1200	8	0
q4w	3	180	6	0
q4w	5	300	10	0

Component 2:

To take into account the potential situation that PDR001 in combination is substantially more toxic than when administered as single agent, a second high-toxicity prior component with vague bivariate normal distribution is added to improve the robustness of the final prior. The parameters of this weekly informative prior distribution are described below:

- Given the relationship defined in Section 14.3.1, here it is assumed that the odds of DLT has dose proportionality, and the median probability of DLT at the reference dose 300 mg (q3w) is 0.10. This corresponds to the mean of $log\left(\beta_{(c2)}^{PDR}\right)$ =0 and the mean of $log\left(\alpha_{(c2)}^{PDR}\right) = -2.20$, which results in the median probability of DLT at 100 mg, 300 mg and 900 mg (q3w) are 0.04, 0.09 and 0.25, respectively.
- The standard deviations of $log\left(\alpha_{(c2)}^{PDR}\right)$ and $log\left(\beta_{(c2)}^{PDR}\right)$ are set to 2 and 1, respectively.
- The correlation between $log\left(\alpha_{(c2)}^{PDR}\right)$ and $log\left(\beta_{(c2)}^{PDR}\right)$ is set to 0, assuming independence.

14.3.1.2.2 Prior distribution for the interaction parameters

Although no interaction is expected for the two agents, uncertainty remains. Therefore, a normal prior for the log-odds multiplier η centered at 0 is used that allows for both synergistic and antagonistic toxicity.

- η is normally distributed, with mean 0, and standard deviation 0.561
- At the starting dose of 200mg (BID) INC280 in combination with 300mg PDR001 q3w the corresponding distribution for the odds ratio has mean 0 and a 97.5th percentile of log(3) i.e. 3-fold increase in odds of DLT due to interaction compared to no interaction.

14.3.1.2.3 Summary of prior distributions

The prior distributions of the model parameters are summarized in Table 14-11. The prior distribution of DLT rates are summarized in Table 14-12 and Figure 14-1.

[redacted]

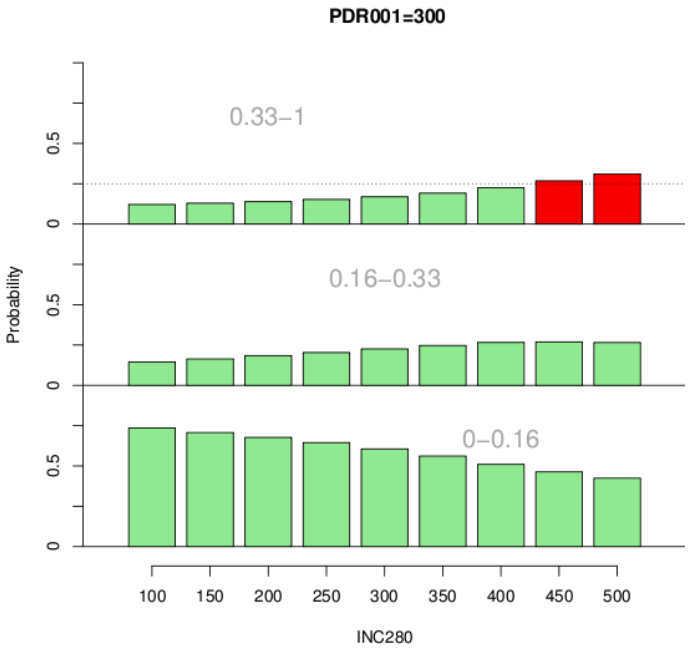
Table 14-11 Prior distribution for the model parameters

Parameter	mean	Standard deviations	correlation	weight
INC280 single agent model				
$(\log(\alpha^{INC}), \log(\beta^{INC}))$ ~ BVN				
(MAP)	(-2.376, 0.06)	(1.053, 1.046)	0.044	1
PDR001 single agent model				
$(\log(\alpha^{PDR}), \log(\beta^{PDR}))$ ~ BVN mixture				
Component 1a (MAP)	(-3.042, -0.496)	(2.246, 1.127)	0.071	0.3504
Component 1b (MAP)	(-4.151, -0.206)	(1.595, 0.773)	-0.179	0.2824
Component 1c (MAP)	(-3.768, -0.713)	(1.175, 0.978)	0.107	0.1672
Component 2 (high-tox)	(-2.197, 0)	(2, 1)	0	0.2
Interaction parameter				
Normal				
η	0	0.561	N/A	N/A

Table 14-12 Summary of prior distribution of DLT rates

INC280 dose (mg)	Prior probabilities that P(DLT) is in the interval :			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
In combination with PDR001 300 mg								
INC280=100	0.735	0.144	0.121	0.143	0.184	0.004	0.072	0.739
INC280=150	0.707	0.164	0.129	0.153	0.185	0.006	0.083	0.745
INC280=200	0.677	0.184	0.139	0.164	0.187	0.008	0.094	0.751
INC280=250	0.645	0.203	0.152	0.175	0.189	0.01	0.106	0.759
INC280=300	0.605	0.226	0.169	0.189	0.192	0.013	0.12	0.77
INC280=350	0.562	0.247	0.192	0.204	0.196	0.016	0.136	0.779
INC280=400	0.51	0.266	0.224	0.223	0.202	0.019	0.156	0.797
INC280=450	0.463	0.269	0.268	0.247	0.214	0.02	0.177	0.823
INC280=500	0.424	0.265	0.311	0.272	0.23	0.02	0.199	0.863

Figure 14-1 Probabilities of under dosing, target toxicity and excessive toxicity of the INC280 dose level (mg, BID) in combination with PDR001 300mg q3w



14.3.1.3 Incorporation of data from ongoing studies

Description of direct down-weighting approach

The dose-DLT information generated from ongoing relevant studies, called co-data, can be incorporated into the BLRM using a direct down-weighting method that accounts for between-trial heterogeneity of data (Neuenschwander et al 2010).

The weight w ($0 < w < 1$), which will be applied to each patient from one particular study, is given by

$$w = \frac{1}{1 + 2n\tau^2/\sigma^2} = \frac{1}{1 + 2n/n^*_\infty},$$

where n is the sample size of this set of co-data, σ is the "outcome standard deviation" for individual observations, and τ is the between-study standard deviation. n^*_∞ is the maximum prior effective sample size under infinite historical information. Let $\sigma = 2$; τ will be chosen depending on the degree of between-study heterogeneity. Table 14-13 provides the values of n^*_∞ and τ corresponding to different levels of between-study heterogeneity given $\sigma = 2$.

[redacted]

Table 14-13 Specification of the maximum prior effective sample size under infinite historical information and the between-study standard deviation given the level of between-study heterogeneity

Heterogeneity	n^*_∞	τ
Small	256	0.125
Moderate	64	0.25
Substantial	16	0.5
Large	4	1
Very large	1	2

Ongoing studies and data

CEGF816X2201c is an ongoing phase II, multicenter, open-label study that includes the investigation of INC280 in combination with Nivolumab in adult patients with cMet positive non-small cell lung cancer.

Prior to each dose escalation meeting, the 6-week post-baseline AE data will be reviewed to identify the events that potentially meet the DLT criteria defined in this protocol (Section 6.2.4). Nivolumab dose level conversion will follow the equation specified for PDR001 in Section 14.3.1.1.1. The cumulative combination dose-DLT data will then be incorporated into the BLRM using the direct down-weighting approach. Let $\sigma = 2$ and $\tau = 1$ to cover account for a large between-trial heterogeneity.

14.3.1.4 Hypothetical on-study data scenarios

To illustrate the performance of the Bayesian model used to guide dose escalation, hypothetical dose escalations scenarios following the provisional dose levels specified in Table 14-14 are displayed. In each case, the maximum dose that can be used in the next cohort of patients is shown. This maximum dose is determined using the model based assessment of the risk of DLT in future patients and the dose escalation rules as described in Section 6.2.3. In practice a dose below the maximum might be chosen based on additional safety, PK or PD information (Section 6.2.3).

Table 14-14 Hypothetical dose escalation scenarios

Scenario	INC280 BID dose (mg) (PDR001 300mg q3w fixed)	Number of patients	Number of DLTs	Next INC280 BID dose level: Dose (mg)	Median P(DLT)	P(excessive toxicity)
1	200	3	0	400	0.114	0.097
2	200	3	1	200	0.168	0.197
3	200 400	3 6	0 1	400	0.129	0.053

[redacted]

Scenario	INC280 BID dose (mg) (PDR001 300mg q3w fixed)	Number of patients	DLTs	Next INC280 BID dose level Dose (mg)	Median P(DLT)	P(excessive toxicity)
4	200	3	0			
	400	5	2			
				300	0.165	0.105
5	200	3	0			
	400	5	2			
	300	4	0			
				400	0.184	0.123
6	200	3	1			
	200	4	0			
				400	0.162	0.148
7	200	3	1			
	200	4	0			
	400	6	1			
				400	0.161	0.083
8	200	3	1			
	200	4	1			
				200	0.189	0.173
9	200	3	1			
	200	4	1			
	200	3	0			
				400	0.210	0.225
10	200	3	1			
	200	4	1			
	200	3	0			
	400	6	1			
				400 (MTD)	0.192	0.116

14.3.1.1 Operating characteristics

Scenarios

In order to investigate the performance of the model, 4 hypothetical scenarios are considered:

1. Scenario 1 represents a scenario which is in line with the prior, i.e. the true underlying toxicity is set to the median values of the prior.
2. Scenario 2 represents a scenario assuming low toxicity than that of the prior
3. Scenario 3 represents a scenario assuming high toxicity than that of the prior
4. Scenario 4 represents a scenario assuming extremely high toxicity, i.e. the true underlying toxicity is set to values between 0.4 and 0.5.

[redacted]

Table 14-15 True underlying probabilities of DLT for different scenarios

INC280 (mg) ***(with PDR001 300mg)***	**100**	**150**	**200**	**250**	**300**	**350**	**400**	**450**	**500**
DLT rate									
Scenario1 (prior):	0.072	0.083	0.094	0.106	0.120	0.136	0.156	0.177	0.199
Scenario 2 (low tox):	0.049	0.057	0.065	0.073	0.083	0.095	0.110	0.125	0.142
Scenario 3 (high tox):	0.134	0.153	0.172	0.192	0.214	0.239	0.270	0.301	0.390
Scenario 4 (extremely high tox):	0.41	0.42	0.43	0.44	0.45	0.46	0.47	0.48	0.49

Simulation details

1000 trials were simulated for each scenario and the total minimum number of DLT to control the declaration of MTD was fixed to one. For the simulated escalation, the next dose selected is the one maximizing the probability of the true DLT rate being in the targeted toxicity interval (16%, 33%] whilst fulfilling the EWOC criterion.

The starting dose was chosen as 200mg INC280 in combination with 300mg PDR001. PDR001 dose is fixed.

Dose escalation continued until MTD was identified, that is, the following conditions were met:

- At least 6 patients have been treated at the dose and
- The dose satisfies one of the following conditions:
  - The posterior probability of targeted toxicity at this toxicity at this dose exceeds 50% and is the highest among potential doses, or
  - A minimum of 12 patients have already been treated on the trial.

Otherwise, a trial could stop before MTD declaration if all dose levels did not satisfy the EWOC criterion or the maximum number of patients defined below had been treated.

The number of patients to treat was defined as:

- Minimum cohort size: 3
- Minimum of patients treated: 12
- Maximum number of patients treated: 60

[redacted]

Simulation results

Metric to assess operating characteristics

Operating characteristics are reviewed based on the simulation results under the three scenarios. The metrics reviewed are:

1. Average proportion of patients receiving a target dose on study (I).
2. Average proportion of patients receiving a dose with true P(DLT) ≥ 33% on study (II).
3. Average proportion of patients receiving a dose with true P(DLT) < 16% on study (III).
4. Probability of recommending a target dose as the MTD (correct final decision) (IV).
5. Probability of recommending a dose with true P(DLT) ≥ 33% as the MTD (patient risk) (V).
6. Probability of recommending a dose with true P(DLT) < 16% as the MTD (VI).
7. Probability of stopping a trial before declaring MTD because all doses levels are too toxic (Stopped).

Operating characteristics

Table 14-16 below summarizes the operating characteristics of the design under the four scenarios.

Table 14-16 Simulation results

Scenario	I	II	III	IV (Target MTD)	V (Overdose MTD)	VI (Under-dose MTD)	Stopped (all too toxic)
1	0.389	0	0.611	0.754	0	0.209	0.037
2	0	0	1	0	0	0.981	0.019
3	0.867	0.109	0.024	0.687	0.147	0.005	0.161
4	0	1	0	0	0.131	0	0.869

The simulation operating characteristics presented show that the combination model performs well under the hypothetical scenarios investigated.

Scenario 4 displays the results of the simulation of high toxicity at all dose levels. Results of the simulation should be interpreted with caution as this simulation does not allow for dose escalation decisions taken outside of the model as defined in Section 6.2.3.2. In particular, if 2 patients experiencing a DLT at a previously untested dose, recruitment to that cohort will cease and either the next cohort will be enrolled at a lower dose, or the dose escalation will end if no dose is identified as safe by the BLRM. For this reason, the scenario is considered liable to overestimate the number of patients that would be treated on a trial in which all doses are overly toxic. Even with this limitation, it is notable that the average proportion of patients expected to be treated on trial is low, and the model correctly identifies in a high proportion of cases (86.9%) that the dose escalation should be stopped.

[redacted]

14.3.2 Bayesian logistical model for the primary analysis of ORR

Main model

A Bayesian logistic regression model with treatment (combination vs. single agent), region (Asian vs. non-Asian), and interaction of treatment and region as covariates will be applied to the primary analysis. The main model is described explicitly as following:

$$\text{logit}(ORR) = \alpha + \beta_1 * \text{treatment} + \beta_2 * \text{region} + \beta_3 * \text{treatment} * \text{region}$$

with α, β_1, β_2, and β_3 the model parameters.

Prior specification

A priori the following assumptions are made:

- No region effect regardless of treatment
- No treatment effect differentiated by region (i.e. no region-treatment interaction)
- ORR = 20% in patients treated with PDR001 single agent
- The odds ratio ($ORR_{PDR001+INC280}$ to ORR_{PDR001}) is 2

Then weakly informative normal priors are assumed for the model parameters with the means corresponding to the above information, and standard deviations 5:

- $\alpha \sim N(\text{logit}(0.2), 5)$
- $\beta_1 \sim N(\exp(2), 5)$
- $\beta_2 \sim N(0, 5)$
- $\beta_3 \sim N(0, 5)$

Inference summary

Posterior mean, SD, 2.5%, 50% and 97.5% quantiles of each model parameter (or its transformation as appropriate) will be provided.

Based on the main model, if the posterior probability of either $\exp(\beta_2)>1$ or $\exp(\beta_2)<1$ is greater than 0.8, it is considered as the evidence of region effect. If the posterior probability of either $\exp(\beta_3)>1$ or $\exp(\beta_3)<1$ is greater than 0.8, it is considered as the evidence of interaction between region and treatment.

Analysis with evidence of region-treatment interaction

If there is evidence of interaction between region and treatment, ORR will be summarized by region. If for a region the posterior probability that odds ratio ($ORR_{PDR001+INC280}$ to ORR_{PDR001}) >1 (i.e. $\exp(\beta_1)>1$) is greater than 0.8, AND the observed $ORR_{PDR001+INC280}$ is at least 10% greater than the observed ORR_{PDR001}, it will be concluded that the combination treatment has a superior anti-tumor effect compared to the PDR001 single agent treatment in the patients from this region.

The ORRs will be estimated and summarized by treatment and by region. The posterior mean and 95% credible interval of $ORR_{PDR001+INC280}$ and ORR_{PDR001} for each region will be provided, respectively. The posterior probabilities of ORR in the following efficacy intervals will be calculated:

- [0, 20%) no anti-tumor activity

[redacted]

- [20%, 100%] clinically relevant anti-tumor activity

The means and 95% credible intervals of treatment effect in odds ratio for each region will be provided.

Analysis without evidence of region-treatment interaction

If there is no evidence of interaction between region and treatment, an analysis with all patients using the following model (with prior distributions specified above) should be applied:

$$\text{logit}(ORR) = \alpha + \beta_1 * \text{treatment} + \beta_2 * \text{region}$$

Posterior mean, SD, 2.5%, 50% and 97.5% quantiles of each model parameter (or its transformation as appropriate) will be provided.

If the posterior probability that odds ratio ($ORR_{PDR001+INC280}$ to ORR_{PDR001}) >1 (i.e. $\exp(\beta_1)>1$) is greater than 0.8, AND the observed $ORR_{PDR001+INC280}$ is at least 10% greater than the observed ORR_{PDR001}, it will be concluded that the combination treatment has a superior anti-tumor effect compared to the PDR001 single agent treatment.

The ORRs will be estimated and summarized by treatment and by region. The posterior mean and 95% credible interval of $ORR_{PDR001+INC280}$, ORR_{PDR001} will be provided. The posterior probabilities of each ORR in the following efficacy intervals will be calculated:

- [0, 20%) no anti-tumor activity
- [20%, 100%] clinically relevant anti-tumor activity

The means and 95% credible intervals of treatment effect in odds ratio (i.e. $\exp(\beta_1)$) and the region effect in odds ratio (i.e. $\exp(\beta_2)$) will be provided.

Analysis without evidence of region effect and region-treatment interaction

If there is evidence of neither region effect nor interaction between region and treatment, an analysis with all patients using the following model (with prior distributions specified above) should be applied:

$$\text{logit}(ORR) = \alpha + \beta_1 * \text{treatment}$$

Posterior mean, SD, 2.5%, 50% and 97.5% quantiles of each model parameter (or its transformation as appropriate) will be provided.

If the posterior probability that odds ratio ($ORR_{PDR001+INC280}$ to ORR_{PDR001}) >1 (i.e. $\exp(\beta_1)>1$) is greater than 0.8, AND the observed $ORR_{PDR001+INC280}$ is at least 10% greater than the observed ORR_{PDR001}, it will be concluded that the combination treatment has a superior anti-tumor effect compared to the PDR001 single agent treatment.

The ORRs will be estimated and summarized by treatment. The posterior mean with 95% credible interval of $ORR_{PDR001+INC280}$ and ORR_{PDR001} will be provided. The posterior probabilities of each ORR in the following efficacy intervals will be calculated:

- [0, 20%) no anti-tumor activity
- [20%, 100%] clinically relevant anti-tumor activity

The mean and 95% credible interval of treatment effect in odds ratio (i.e. $\exp(\beta_1)$) will be provided.

[redacted]

14.4 Appendix 4: Recommended management algorithms for suspected toxicities

These general guidelines for management of toxicities (Postow et al 2015 - supplementary appendix) constitute guidance to the Investigator and are not intended to substitute institutional standard of care practice. The guidance applies to all 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.

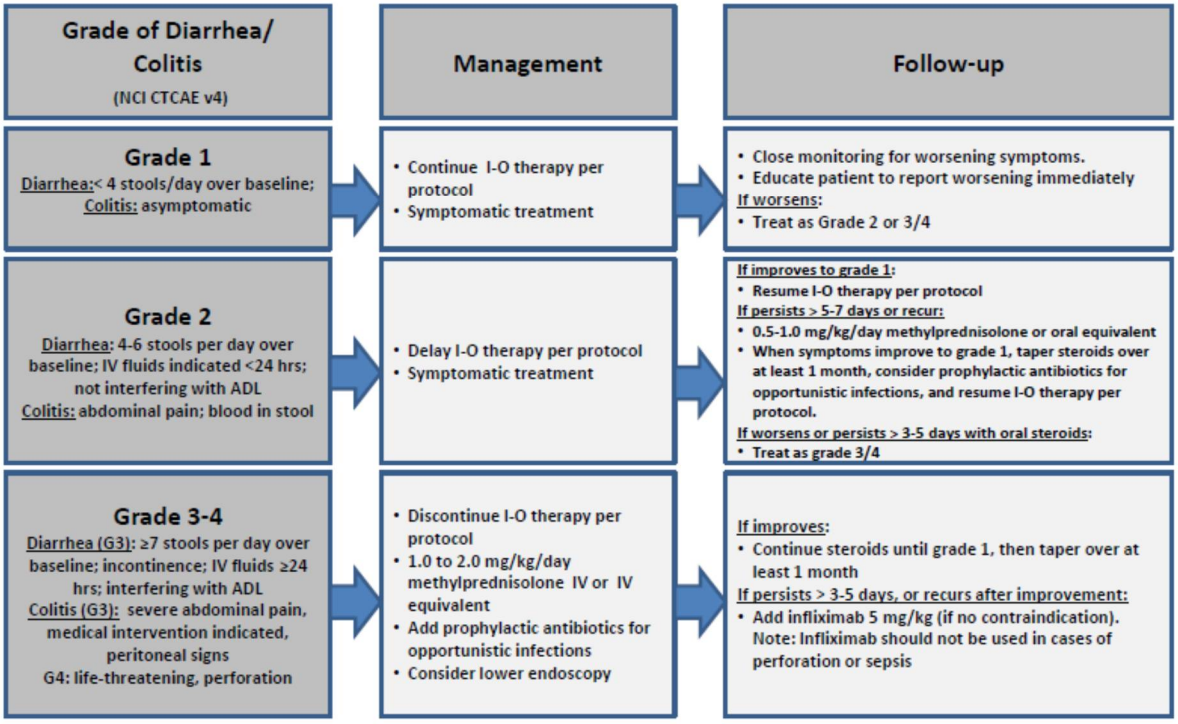
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

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.

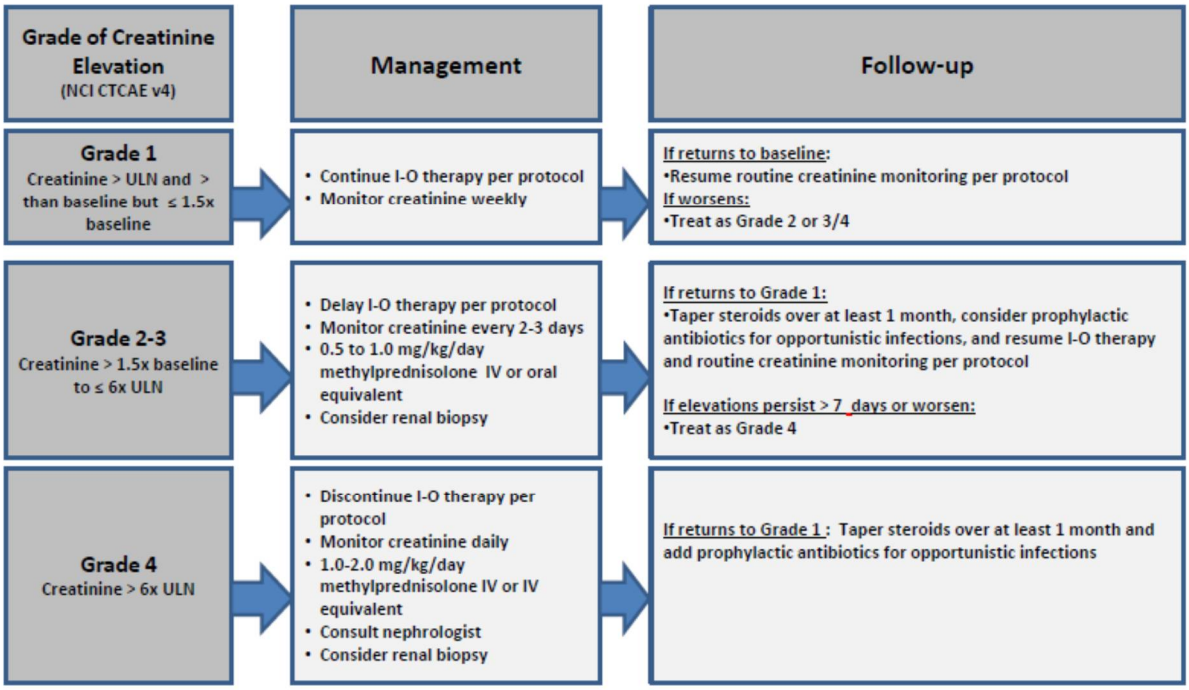


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

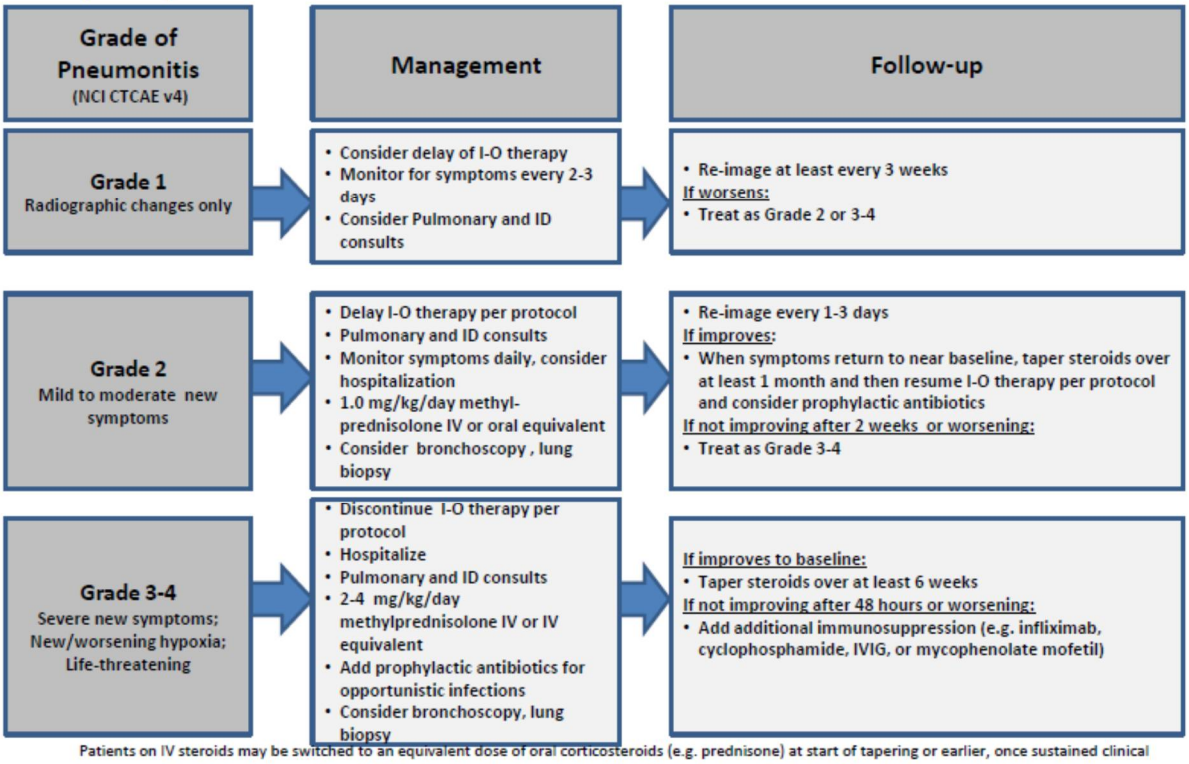


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of 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.

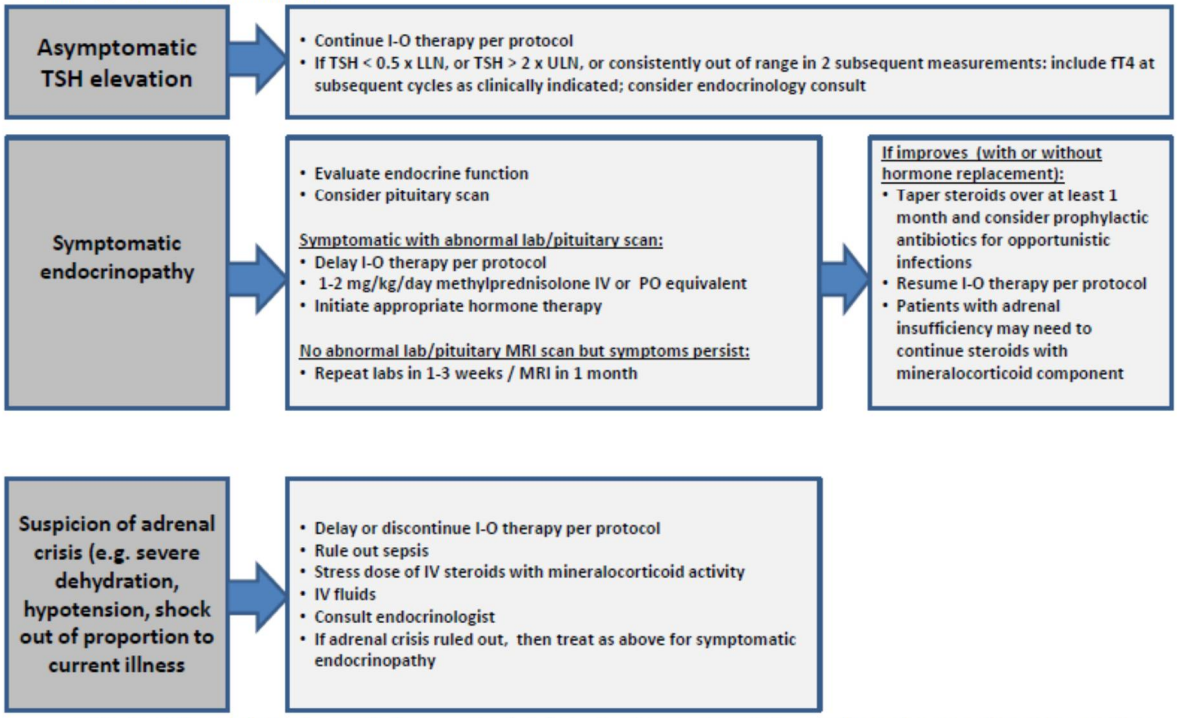


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[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.

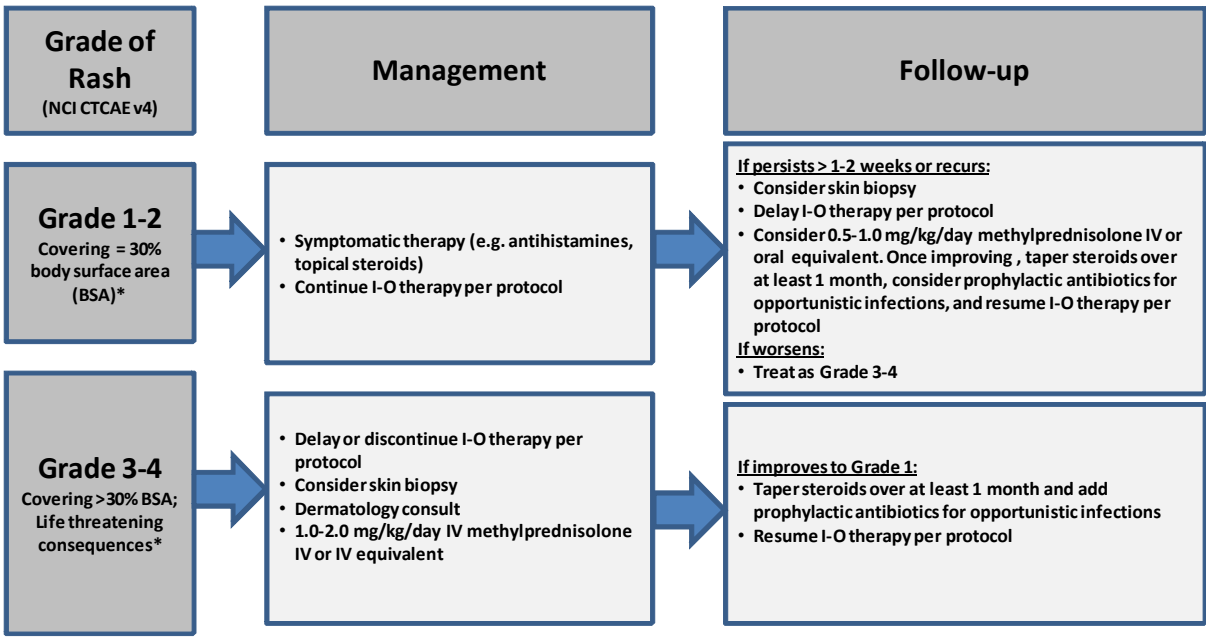


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

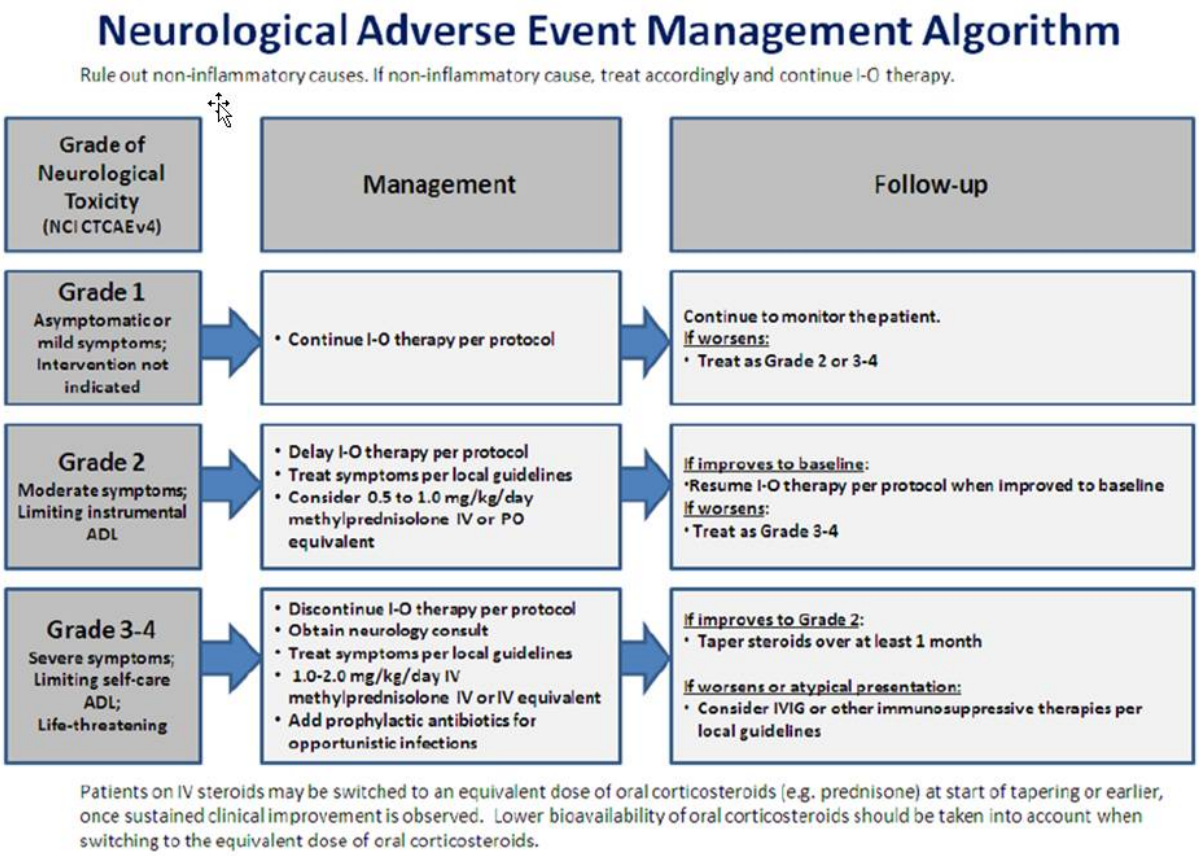
Skin Adverse Event Management Algorithm

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.

[redacted]



14.4.1 References (available upon request)

Postow MA, Chesney J, Pavlick AC, et al (2015). Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med.;372(21):2006-17 (supplementary appendix).

[redacted]

14.5 Appendix 5: Prohibited concomitant medication for patients in INC280 + PDR001 combination arm

If a medication is listed in Table 14-17 and Table 14-18/Table 14-19, more stringent practice shall be applied (that is, the medication shall be prohibited as in Table 14-17)

Table 14-17 Drugs prohibited while on study

Mechanism of Interaction	Drug Name
Strong CYP3A4 inducer	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampin, mitotane, St. John's wort (*Hypericum perforatum*)
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies". This may not be an exhaustive list, will be updated periodically. Note: If a medication is listed more than once, the more stringent practice shall be applied (that is, the medication shall be prohibited).	

[redacted]

14.6 Appendix 6: Concomitant medication to be used with caution for patients in the INC280 + PDR001 combination arm

Table 14-18 Drugs with a known risk of torsades de pointes

TdP Risk	Generic names
Known	amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib
Check crediblemeds.org/healthcare-providers/drug-list for the most updated list. This may not be an exhaustive list, will be updated periodically.	

Table 14-19 Drugs to be used with caution while on study

Mechanism of Interaction	Drug Name
Strong CYP3A inhibitor	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
CYP1A2 substrate with NTI	theophylline, tizanidine
CYP2C9 substrate with NTI	Phenytoin, warfarin
CYP2C19 substrate with NTI	(S)-mephenytoin
P-gp substrates	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, atorvastatin, azithromycin, boceprevir, bosentan, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine, dabigatran, digoxin, docetaxel, domperidone, doxepin, doxorubicin, eribulin, everolimus, fentanyl, fexofenadine, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, levofloxacin, linagliptin, linezolid, loperamide, losartan, maraviroc, mirabegron, moxifloxacin, nadolol, naloxegol, nateglinide, nevirapine, nintedanib, olodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, proguanil, posaconazole, pravastatin, quinidine, ranolazine, ritonavir, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole,
BCRP substrates	atorvastatin daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinylestradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
H_2-receptor antagonists	ranitidine, nizatidine, famotidine, cimetidine
Proton pump inhibitor	esomeprazole, pantoprazole, Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole, dexlansoprazole

[redacted]

Mechanism of Interaction	Drug Name
Antacids	aluminum hydroxide, aluminum carbonate, calcium hydroxide, calcium carbonate, bismuth subsalicylate
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies". This may not be an exhaustive list, will be updated periodically. NTI: narrow therapeutic index. Note: If a medication is listed more than once, the more stringent practice shall be applied (that is, the medication shall be prohibited).	

[redacted]

14.7 Appendix 7: Child-Pugh classification of severity of liver disease

Child-Pugh classification system

The CPC is used to assess the severity of impaired hepatic function in patients with liver cirrhosis (Child and Turcotte 1964, FDA guidance 2003). In general, it is used to determine the risk to a patient with regard to the treatment(s) (e.g. surgery, transplant, medication), and, to suggest the perceived survival of the patient over a period of time.

Hepatocellular carcinoma patients who have Child-Pugh grade A score (5 - 6 points) at the baseline screening are eligible for participating in Study [CINC280X2201], provided that the patients meet all other eligibility criteria.

Calculation and interpretation for Child-Pugh scores

The severity of liver disease is based on the CPC criteria, which will be calculated based on clinical findings and laboratory results during the screening period. Five variables are considered (severity of ascites, hepatic encephalopathy, abnormality in serum bilirubin, serum albumin and clotting times).A score (between 1 and 3) is accordingly assigned to each of these factors (Table 14-20). The sum of the scores provides the Child-Pugh score, which corresponds to a Child-Pugh grade (or Child's grade) of A, B or C (Table 14-21).

Table 14-20 Child-Pugh score calculation

Variables	Points assigned			Units
	1	2	3	
Total Bilirubin	< 2 (<34)	2-3 (34-50)	> 3 (>50)	mg/dL (µmol/L)
Serum Albumin	> 35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)	g/L (g/dL)
PT (or INR)	< 4 (< 1.7)	4-6 (1.7-2.30)	> 6 (>2.30)	sec (no unit)
Ascites	Absent	Slight	Moderate	no unit
Hepatic Encephalopathy*	None	Grade 1-2	Grade 3-4	no unit

*Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
*Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
*Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
*Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
*Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Table 14-21 Child-Pugh score interpretation

Severity (grade)	Child-Pugh Score
A	5 - 6
B	7 - 9
C	10 - 15

14.7.1 References (available upon request)

Child CG, Turcotte JG (1964). Surgery and portal hypertension. In: The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders:50-64

FDA Guidance for industry (2003). Pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling

[redacted]