NOVARTIS

Clinical Development

PDR001

Protocol CPDR001X2201 / NCT02605967

A phase II, open-label, randomized controlled study of PDR001 in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic nasopharyngeal carcinoma who progressed on standard treatment

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List of abbreviations

Abs	Antibodies
(m)OS	(median) Overall Survival
(m)PFS	(median) Progression Free Survival
(m)TTP	(median) Time to Progression
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
APTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CMO&PS	Chief Medical Office and Patient Safety
CRO	Contract Research Organization
CRP	c-Reactive protein
CRS	Cytokine Release Syndrome
CRT	Chemoradiotherapy
CSF	Colony Stimulating Growth Factor
CSR	Clinical Study report
DC	Dendritic Cell
DOR	Duration of Response
EBV	Epstein Barr Virus
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
ELISA	Enzyme Linked Immunosorbent Assay
ESA	Erythropoiesis Stimulating Agents
eSAE	Electronic Serious Adverse Event
FAS	Full Analysis Set
Foxp3	Forkhead box P3
HAART	Highly Active antiretroviral Therapy
HbcAg	Core Antigen to Hepatitis B
HBsAg	Surface Antigen of the Hepatitis B
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HR	Hazard Ratio
i.v.	Intravenous(ly)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
IHC	Immunohistochemistry
IL-1	Interleukin-1
IL-6	Interleukin-6
INR	International Normalized Ratio
irAE(s)	Immune-related Adverse Event(s)
IRB	Institutional Review Board

irPD	Immuno-related Progressive Disease
irPFS	Immune-related Progression Free Survival
irRC	Immune-related Response Criteria
IRT	Interactive Response Technology
LAG-3	Lymphocyte Activation gene-3
LLOQ	Lower Limit Of Quantitation
LMP1	Latent Membrane Protein 1
LMWH	Low Molecular Weight Heparin
mAb(s)	Monoclonal Antibody(ies)
MDSC	Myeloid-derived Suppressor Cell
MLR	Mixed Lymphocyte Reaction
MTD	Maximum Tolerated Dose
NKT cells	Natural Killer T cells
NPC	Nasopharyngeal cancer
NSCLC	Non-Small Cell Lung Carcinoma
ORR	Overall Response Rate
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
Per os	Oral administration
PK	Pharmacokinetics
PPOS	Predictive Probability of Success
PPS	Per Protocol Set
PR	Partial Response
PT	Prothrombin time
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumors
RF	Rheumatoid factor
RP2D	Recommended phase II dose
SAE(s)	Serious Adverse Event(s)
SEB	Staphylococcal enterotoxin B
SJS	Stevens Johnson Syndrome
TEN	Lyell syndrome/toxic epidermal necrolysis
TIL(s)	Tumor Infiltrating Lymphocyte(s)
TIM-3	T-cell immunoglobulin domain and mucin domain-3
TNF-α	Tumor necrosis factor-alpha
Tregs cells	Regulatory T cells
TSH	Thyroid Stimulation Hormone
WHO	World Health Organization

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 patient
Control arm/Comparator drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number (Patient No.)	A unique identifying number assigned to each patient/ who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening/baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
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
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient 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 study treatment for any reason
Supportive treatment (Concomitant medications)	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Withdrawal of consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data

Protocol summary

Protocol number	CPDR001X2201
Title	A phase II, open-label, randomized controlled study of PDR001 in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic nasopharyngeal carcinoma (NPC) who progressed on standard treatment.
Brief title	Phase II study of PDR001 in patients with nasopharyngeal carcinoma.
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this randomized controlled Phase II study is to assess the efficacy of PDR001 versus investigator's choice of chemotherapy in patients with NPC. By blocking the interaction between PD-1 and its ligands, PD-L1, PDR001 inhibits the PD-1 immune checkpoint, resulting in activation of an antitumor immune response by activating effector T-cells and inhibiting regulatory T-cells.
Primary Objective(s)	Progression free survival (PFS) as per RECIST v1.1
Secondary Objectives	● Evaluate anti-tumor activity of PDR001 vs investigator's choice of chemotherapy (OS, ORR, DOR, TTP, irPFS) ● Characterize the safety and tolerability of PDR001 ● Characterize the pharmacokinetic profile of PDR001 ● Assess emergence of anti-PDR001 antibodies ● Assess pharmacodynamic effect of PDR001 in peripheral blood
Study design	This is an open-label, multi-center, randomized, controlled phase II study to evaluate the efficacy and safety of PDR001 versus investigator's choice of chemotherapy in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic NPC who progressed on or after first-line platinum-based treatment. PDR001 will be administered every 4 weeks until patient experiences unacceptable toxicity, progressive disease per immune related Response Criteria (irRC) and/or treatment is discontinued at the discretion of the investigator or the patient. A cycle is defined as 28 days.
Population	The study will be conducted in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic NPC who progressed on or after first- line platinum-based therapy.

Inclusion criteria (selected)	1. Histologically documented non-keratinizing locally advanced recurrent or metastatic NPC. 2. Must be resistant to platinum-based chemotherapy (defined as progression on or after platinum-based chemotherapy given in the recurrent/metastatic setting). 3. May have received at least 1 prior therapy for recurrent or metastatic disease, up to 2 prior systemic therapies. 4. An archival tumor specimen or newly obtained tumor sample may be submitted at screening/baseline (a fresh tumor sample is preferred), unless agreed differently between Novartis and the Investigator. 5. At least 1 measurable lesion (as per RECIST v1.1) progressing or new since last anti-tumor therapy. 6. Prior treated brain or meningeal metastases must be without MRI evidence of progression for at least 8 weeks and off systemic steroids for at least 2 weeks prior to screening/baseline. 7. Patient must be willing to undergo testing for human immunodeficiency virus (HIV) if not tested within the past 6 months. If HIV+ positive, patient will be eligible if: his/ her CD4+ count ≥ 300/μL; his/her viral load is undetectable; he/she is currently receiving highly active antiretroviral therapy (HAART).
Exclusion criteria (selected)	1. History of severe hypersensitivity reactions to other mAbs 2. Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved asthma/atopy that is treated with broncho-dilators. 3. Active HBV or HCV infections requiring therapy. 4. Prior PD-1- or PD-L1-directed therapy 5. Patients receiving systemic treatment with any immunosuppressive medication. 6. Use of any vaccines against infectious diseases (e.g. varicella, pneumococcus) or investigational therapeutic cancer vaccines within 4 weeks of initiation of study treatment.
Investigational and reference therapy	PDR001 Investigator's choice of chemotherapy
Efficacy assessments	Tumor assessment per RECIST v1.1 and per irRC
Safety assessments	Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs
Other assessments	Serum PK parameters and Immunogenicity Pharmacodynamic assessment on pre- and post- treatment on tumor and blood samples
Data analysis	The primary analysis of PFS will be performed for the comparison of PDR001 with the control arm (investigator's choice of chemotherapy), after approximately 70 PFS events have occurred across both of the two arms combined. A final clinical data analysis will be performed once all patients have discontinued the study or at the end of the study (end of survival follow up period), whichever occurs first
Key words	Phase II, PDR001, Checkpoint inhibitor, PD-1, PD-L1, nasopharyngeal cancer

Amendment 06 (24-Jun-2019)

Amendment rationale

The main purpose of this protocol amendment is to revise 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.

In addition, the blood sample collection is removed for the assessment of serum cytokines used for retrospective analysis of a cytokine release syndrome adverse event. Blood samples for serum cytokines were included due to the unknown risk of CRS with IO agents alone and in combination, and to allow an assessment of any association between cytokines and clinical events. These samples have been drawn at baseline and at the time of a potential CRS event, stored, and analyzed retrospectively. Due to this, results are not intended to be used to support clinical decision-making for patients with possible CRS. There were no unexpected clinically assessed events of CRS observed across 19 studies including more than 2200 patients. The risk of CRS in the current study is deemed to be low, thus supporting the removal of this blood sample collection.

Study status

The study enrolment was completed with the last patient first dose on 03-Aug-2018. In total 122 patients have been randomized, including 82 patients randomized to the PDR001 arm. As of 21-May-2019, there are 12 ongoing patients, all of which are on PDR001 treatment. Among the 12 patients, 11 were randomized to PDR001 arm, and one was randomized to chemotherapy arm and then crossed over to receive PDR001 treatment.

Changes to the protocol

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

Section 4.3 Definition of end of the study: addition of language to account for patients who would transfer into another study or an alternative treatment option to continue provision of study treatment.

Section 6.2.4 Management of toxicities and irAEs and Table 6-2 Criteria for interruption, delay, re-initiation and discontinuation of PDR001: removal of blood sample collection for retrospective central analysis of safety cytokines in case of suspected CRS.

Table 7-1 and Table 7-3 Visit evaluation schedule (PDR001, Crossover): addition of footnotes to clarify the assessments within follow-up period are not applicable to patients who transfer to another study or an alternative treatment option to continue provision of study treatment.

Table 7-1, Table 7-3 Visit evaluation schedule (PDR001, Crossover) and Table 7-6 Clinical lab parameters collection plan: addition of footnotes to clarify termination of safety cytokine sample collection upon implementation of Protocol amendment 06.

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.

Section 7.1.5, 7.1.6, 7.1.7 Follow up for safety evaluations, disease progression, survival: addition of language to specify that patients who transfer to another study or alternative treatment option to continue provision of study treatment will not complete safety, disease progression and/or survival follow up.

IRBs/IECs

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

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

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

Amendment 05 (30-Aug-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 occurrence of a case of Steven 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 TEN. This change has already been implemented as part of an urgent safety measure released on 15 June 2018. This protocol amendment is now finalizing 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 6-2). Changes to other sections of the protocol have been made to align with the updated dose modification section.
- 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.
- The independent central review of imaging data will be terminated for the whole study when both criteria are met, 1) decisions are made based on central review results for all chemotherapy arm patients on whether to crossover; 2) all patient have reached a minimum of 12 months follow up after the first dose of study treatment (unless have been lost to follow-up). Because the purposes of applying the central review service will have been fulfilled.
- 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. The available safety data from clinical studies indicate that PDR001 is generally well tolerated.
- In this amendment, ECG will no longer be centrally reviewed. Sites will continue to perform local review of ECG following local practice or as clinically indicated. The reason is the data analyzed to date indicate PDR001 does not have a clinically relevant QT liability and support reduced ECG monitoring scheme for future clinical studies, as outlined in Section 7 of ICH E14 (PDR001 IB version 7.1).
- PK and IG sample collection will be terminated after the Cycle 4 samples have been collected from all the PDR001 arm patients, as sufficient PK and IG samples have been collected for characterization of the PK and IG profile of PDR001 in NPC patients.
- To simplify study conduct, all language related to CSR timing has been removed.
- Additional editorial changes have been made to sections where previous language was deemed inaccurate or ambiguous.

Study status

The study enrolment was completed with the last patient first dose on 3 Aug 2018. In total 122 patients have been randomized, including 82 patients randomized to the PDR001 arm. As of 10

August 2018, there are 27 ongoing patients, among which 18 are on PDR001 treatment, 5 are on Chemotherapy, and 4 are crossover patients.

Changes to the protocol

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

List of abbreviations: Added SJS and TEN.

Glossary of terms: Added term "Personal data" and updated term "Withdrawal of consent".

Table 6-2: Language has been added to mandate permanent study treatment discontinuation for SJS/TEN, as per the USM letter dated 15 June 2018.

Section 7.1.3 and Section 7.1.4: Updated the withdrawal of consent language.

Section 7.2.1: Specified the timing to terminate central imaging review.

Section 7.2.2.5, Table 7-1, Table 7-2, Table 7-3 and Table 7-6: Specified the timing to terminate serology tests.

Section 7.2.2.6, Table 7-1, Table 7-3 and Table 7-7: Specified the timing to terminate central ECG review, and that central ECG review of designated time points will be replaced by local ECG review of time points based on Investigator's judgement.

Section 7.2.3: Updated the timing to terminate PK and IG sample collection.

Section 8.3: Follow-up of newborn has been extended from 3 months to 12 months.

Section 10: Removed the timing of CSR. Section 4.3 is updated accordingly.

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 June 2018. These changes are required for patient 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.

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

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

Amendment 04 (07-Dec-2017)

Amendment rationale

This amendment introduces the addition of safety evaluations on 30 and 90 days to the 150-day safety follow-up visit, in order to ensure regular safety follow-up of patients after the last administration of PDR001.

During the 150-day safety follow-up period, many patients will most likely start a new antineoplastic therapy. In such cases, only AEs and SAEs suspected to be related to PDR001 will be collected in CRF, in order to focus on PDR001 related safety information; and concomitant medications will be recorded in CRF until the 30-day safety follow-up has been completed or the start of a new antineoplastic therapy, whichever occurs first. To ensure a consistent approach in the reporting of the safety profile of study treatment, the main data analysis will focus on the period from the first dose of study treatment to 30 days after the date of the last administration of study treatment. Data collected beyond this period (i.e. post-treatment period) will be summarized separately.

For prohibited concomitant therapy, the wording related to the use of systemic steroid therapy during the course of study is adjusted in order to provide more flexibility for patients who would need such therapy for treatment of acute conditions.

The description of safety summaries is added to the safety data analysis to align with the program level approach.

Immune-related adverse events (irAEs) have been included in the AEs part as secondary endpoints. To avoid redundant description and reporting, the irAEs are removed as standalone secondary endpoint but continue to be analyzed as part of the AEs analysis (secondary endpoint).

Neurological Adverse Event Management Algorithm was inadvertently removed in the last protocol version 03, (dated 27-Jul-2016). Therefore this same algorithm is included back in the current amendment (protocol amendment 04).

Although response rate (by RECIST 1.1) remains important, the meaningful benefit of immunotherapy has thus far been with the impressive durable clinical efficacy. PFS and OS benefits with immunotherapies have been demonstrated for those who do respond, as demonstrated by the 'long tail' on the Kaplan-Meier curve (Sharma and Allison, 2015). Therefore, in order to explore the durability of disease control by PDR001 in patients with NPC, the analysis of long term endpoints will be added to the primary CSR. This analysis will include all patients data up to the date when each patient has reached a minimum of 12 months of follow up after the first dose of study treatment or has been lost to follow-up. There are no changes to the pre-defined study endpoints.

In order to better characterize PK through population approach, one more sample collection is added for PK and IG at the 150-day safety follow-up visit for PDR001 arm patients who come on site.

To align with the EMA standard term list, the PDR001 pharmaceutical form has been updated to “Powder for solution for infusion”.

Additional editorial changes and clarifications have been made to sections where previous language was deemed inaccurate or ambiguous.

Study status

As of the cut-off date 16 October 2017, 114 patients have been randomized, including 76 patients randomized to the PDR001 arm.

Changes to the protocol

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

Section 3 Objectives and endpoints

- Removed irAEs from the Secondary endpoint because they are included in the AEs category.

Section 4.1 Description of study design

- Corrected the end of the 28-day screening period from randomization to C1D1 to be consistent throughout the protocol

Section 4.3 Definition of end of the study

- Added “primary CSR” to be consistent with Section 10.
- Removed the details of data analysis, which have been described in Section 10.

Section 6.1.1 Dosing regimen, Section 6.5 Study drug preparation and dispensation and Section 6.5.1 Study drug packaging and labeling

- Replaced “lyophilisate in vial” with the European Medicines Agency (EMA) standard term "powder for solution for Infusion" to describe the PDR001 pharmaceutical form.

Section 6.3.3 Prohibited concomitant therapy (patients in PDR001 arm)

- Added further information on the use of systemic steroid therapy:
  - For replacement-dose steroids in the setting of adrenal insufficiency, use is acceptable providing this is ≤ 10 mg/day prednisone or equivalent.
  - Use of systemic steroid therapy is authorized for transient exacerbations of other underlying diseases such as chronic obstructive pulmonary disease (COPD) requiring treatment for < 3 weeks.

Section 7.1.5 Follow up for safety evaluations

- Added safety follow-up phone call or visit at 30-, 90-, and 150-day for PDR001 arm and crossover patients. The schedule is also reflected in Table 7-1 and Table 7-3.
- Added sampling for PK and IG at 150-day safety follow-up. It is also reflected in Table 7-8 of section 7.2.3.
- Specified data collection of Concomitant medications during safety follow-up period. It is also reflected in Table 7-1 and Table 7-3.

Section 7.2.2.5 Laboratory evaluations

- Specified female patients of child-bearing potential should perform pregnancy tests every month during and at the end of the safety follow-up period.

Section 8.1.1 Definitions and reporting

- Specified AEs collection after initiation of a new post-treatment antineoplastic therapy during safety follow-up period. It is also reflected in Table 7-1 and Table 7-3.

Section 8.2.2 Reporting

- Removed "SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy)" as it is not applicable to this study.
- Specified SAEs collection after initiation of a new post-treatment antineoplastic therapy.

Section 10 Statistical methods and data analysis

- Specified the endpoints included in the primary analysis.
- Added another analysis including all patients data up to the date when each patient has reached a minimum of 12 months follow up after the first dose of study treatment or has been lost to follow-up.
- Specified that the primary CSR will include both analyses.

Section 10.4.2 Statistical hypothesis, model, and method of analysis

- Added log-rank test

Section 10.5.3.1 Analysis set and grouping for the analyses

- Updated the definition of "on-treatment period" and "post-treatment period" to ensure a consistent approach in the reporting of the safety profile of study treatment
- Added description of the safety summaries in safety analysis.

Section 10.5.3.2 Adverse events (AEs)

- Removed irAEs because they are covered by AEs of special interest category in safety summaries.
- Added description of the safety summaries in safety analysis.

Section 11.5 Publication of study protocol and results

- Updated to reflect latest procedures on the publication of study protocol and results.

Section 14.4 Appendix 4: Management algorithms

- Added Neurological Adverse Event Management Algorithm

IRBs/IECs

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

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

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

Amendment 03 (27-Jul-2016)

Amendment rationale

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 period post PDR001 treatment from 90 days to 150 days. These changes are related to an Urgent Safety Measure communicated on 08-Jun-2016 to all investigators.

This amendment also introduces the following changes.

Clarification of Inclusion Criterion 8: specify that lesions in previously irradiated areas should not be considered measureable unless there is clear evidence of progression in such lesions since the radiotherapy.

Modification of Exclusion Criterion 8: Patients who have previously received an investigational therapeutic cancer vaccine can be eligible. This change has been introduced considering the limited efficacy evidence available for cancer vaccines and the high unmet medical need in this patient population.

Clarification of Exclusion Criterion 10: Patients who have previously received an investigational therapeutic cancer vaccine are eligible providing there is a minimum 4-week washout period between the last dose of the vaccine and the first dose of PDR001.

The ECG monitoring plan is simplified to collection of ECGs at screening, Cycle 1 day 1, Cycle 3 day 1 and as clinically indicated, because no signal of QT interval prolongation was observed in the first in human study (CPDR001X2101) (see PDR001 Investigator's Brochure) or other currently approved anti-PD-1 antibodies (see KEYTRUDA® and OPDIVO® labels). [redacted]

There is a clerical error in the previous version of the protocol within the criteria for discontinuation language in Section 7.1.3 (Discontinuation of study treatment). Amendment 2 equivocally indicated that patients must be discontinued from treatment upon observance of any of the events listed in the section. This section has been clarified by differentiating reasons that may cause treatment discontinuation from those that require mandatory treatment discontinuation.

Clarification of Section 7.2.2.5: serum pregnancy test will be performed at screening/baseline and/or within ≤ 72 hours before first dose of study treatment, day 1 of each cycle and EOT. The change is to align with the latest Novartis guideline on prevention of pregnancies in participants in clinical trials.

Clarification of Section 10.5.5 to immunogenicity data may be analyzed appropriately according to study demand.

Minor changes have been made for consistency and to clarify operational details.

Study status

As of the cut-off date 06-Jun-2016, 2 patients have been enrolled and 1 patient is treated with PDR001 at 400mg i.v. every 4 weeks.

Changes to the protocol

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

Section 4.1 Study Description of study design

- The safety follow-up for patients receiving PDR001 treatment was extended from 90 to 150 days. This change was applied throughout the protocol in Sections 5.3; 7.1.5; 8.1.1; 8.2.2; 10.5.3.1.; Table 7-1 and Table 7-3.

Section 5.2 Inclusion criteria

- Revised criterion 8 to add that lesions in previously irradiated areas should not be considered measureable unless there is clear evidence of progression in such lesions since the radiotherapy.

Section 5.3 Exclusion criteria

- "Any therapeutic cancer vaccine" was removed from exclusion criterion 8.
- Addition of a washout period for investigational therapeutic cancer vaccines in exclusion criterion 10. This specifies that use of investigational therapeutic cancer vaccines within 4 weeks of initiation of study treatment is excluded.

Section 7.1.3 Discontinuation of Study Treatment

- The word "must" has been replaced by the word "may". This sentence "Study treatment may be discontinued under the following circumstances" outlines the reasons that may require treatment discontinuation.
- The criterion "confirmed Complete response as per RECISTv1.1" only requires patients treated with PDR001 to discontinue study treatment.

Section 7.2.2.5 Laboratory evaluations

- Table 7-6 "fasting" was added after "glucose" to clarify glucose tests shall be taken when patients are fasted.
- The serum pregnancy test will be performed at screening/baseline and/or within ≤ 72 hours before first dose of study treatment, day 1 of each cycle and EOT.

Section 7.2.2.6.1 Electrocardiogram (ECG)

- Cardiac assessments Electrocardiogram (ECG) collection has been removed on Cycle 1 D1 pre-dose, Cycle 6 D1 and end of treatment. In addition, Table 7-7; Table 7-1 and Table 7-3 have been updated accordingly.

Section 10.5.5 Immunogenicity-exposure and/or adverse event relationship

- Immunogenicity data may be analyzed appropriately according to study demand. "will" was replaced by "may" in the concentration/adverse event – immunogenicity relationship analysis. "may" was also used to replace "will" in other correlation analysis.

[redacted]

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 related to the urgent safety measure are to be implemented prior to IRB/IEC approval. All other changes described in this amended protocol require IRB/IEC approval prior to implementation.

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

Amendment 02 (21-Jan-2016)

Amendment rationale

The primary purpose of this amendment is to introduce the recommended phase II dose of PDR001 established in the phase I (first-in-human) study CPDR001X2101. Based on pharmacokinetic (PK) and safety data from study CPDR001X2101, the recommended Phase 2 dose (RP2D) for PDR001 has been declared as a flat dose of 400mg i.v. every 4 weeks.

Based on preliminary PK data from study CPDR001X2101 and the possibility of delayed appearance of immune-related adverse events, the safety follow-up period has been extended to 90 days after the last dose of PDR001 treatment.

Patients who are HBV or HCV positive are eligible. As PD-1 blocking antibodies are not immunosuppressive, there is no specific contraindication to recruit patients who are HBV and HCV positive, provided their active disease is adequately controlled by antiviral therapy.

Patients who have previously received CTLA-4-antagonists are eligible providing they don't have hepatic, diarrhea/colitis or endocrine adverse events (AE)s Grade≥2, any other non-laboratory immune-related AE≥3. Patients must have minimum 8 week washout period between the last dose of anti-CTLA4 and the first dose of PDR001. The 8 weeks washout period is needed to resolve the anti-CTLA4 induced irAE, which may have a delayed onset.

To align this protocol with the latest Novartis guidelines for the prevention of pregnancies in participants in clinical trials and their partners, the exclusion criteria were updated to exclude sexually active male subjects who are not willing to use a condom during the study.

For monitoring of thyroid function, the measurement of free T4 a more specific parameter as compared to total T4 is included, whereas total T4 is removed.

The tumor assessment should include the head and neck if clinically relevant.

This amendment also incorporates revision as requested by a regulatory authority to exclude patient with contraindications to the investigator's choice of treatment for the control arm. Investigators must refer to the approved label of the product chosen in the control arm especially regarding contraindications, contraceptives regimens, dosage adjustment in case of toxicity, patient monitoring and prohibited drugs or drugs used with caution.

As all SAEs information is collected and recorded within the Electronic Data Capture (EDC) system, this amendment introduces the electronic Serious Adverse Event (eSAE) reporting method.

Minor changes have been made for consistency and to operations-related specifications.

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 1.3.1.2 PDR001 clinical experience

- Updated doses and regimens evaluated in the CPDR001X2101 study and the recommended phase II dose.

Section 2.3 Rationale for dose and regimen selection

- Updated the RP2D which has been established in CPDR001X2101as a flat dose 400mg i.v. every 4 weeks. This change was applied in Section 2.2; 6.1.1.; 6.2.3; 6.5; 7.1.2.

Section 4.1 Study Description of study design

- The safety follow-up for patients receiving PDR001 treatment was extended from 30 to 90 days. This change was applied throughout the protocol in Sections 7.1.5; 7.2.2.5; 8.1.1; 8.2.2; 10.5.3.1.

Section 5.3 Exclusion criteria:

- Revised criterion 4 to allow patients who are HBV and HCV positive, providing their active disease is controlled by antiviral therapy(local guideline)
- Addition of a washout period for CTLA-4 antagonists in criterion 7
- Addition of total hysterectomy in the definition of female sterilization and update of the definition of highly effective contraception in exclusion criterion 17
- Addition of exclusion criterion 18, which excludes sexually active male patients who do not wish to a condom during intercourse
- Addition of exclusion criterion 19, which excludes patient with contraindications to the chosen treatment per investigator’s choice for the control arm

Section 6.1.4 Chemotherapy treatment (patients in Control arm)

- Addition section to indicate investigator must refer to the approved label of the product used in the control arm especially regarding pre-medication schemes, the contraindications, contraceptives regimens, dosage adjustment in case of toxicity, patient monitoring and the prohibited drugs or drugs used with caution.

Table 7-1 and 7-3 Visit evaluation schedule:

- Updated the safety follow-up from 30 days to 90 days after the last dose of PDR001 treatment, as well as related assessments.
- Visit schedule was incorporated to dose regimen every 4 weeks.

Table 7-2 Visit evaluation schedule:

- Addition of a footnote that investigators must refer to the approved label of the product used in the control arm.

Section 7.1.5 Follow-up period:

- Updated the safety follow-up from 30 day to 90 day follow-up and associated assessments for PDR001 treatment

Section 7.2.1 Efficacy assessments:

- Addition of wording to clarify the disease assessment at screening.

Section 7.2.2.5 laboratory evaluations

- Addition of wording to clarify serum pregnancy test at screening, sequential visits and safety follow-up visit.
- Table 7-6 Free T4 has replaced Total T4.

- Table 7-8 PK sample time point was updated according to the dosing frequency of every 4 weeks.

Table 7-9 Biomarker sample collection-plan

- Removal of the example of IFN-gamma being assessed in tumor biopsies, as this parameter might no longer be analyzed in this context, but only as soluble cytokine in plasma.

Section 8.2.2.Reporting

- Introduced the electronic Serious Adverse Event (eSAE) reporting method as all SAEs information would be collected and recorded within the Electronic Data Capture (EDC) system instead of paper SAE form.

Section 8.3 Pregnancies

- Addition of wording of pregnancy outcomes collection for the female partner of any male participant.

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

- The lesion diameter measurements under RECIST 1.1 and irRC are the long axis (or longest diameter) for non-nodal lesions and the short axis for the nodal lesions. Sections 14.2.2, 14.2.3 and Table 14-6 were updated to clarify that assessments are not based only on longest diameters.

IRB/IEC/HA

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

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

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

Amendment 01 (09-Nov-2015)

Amendment rationale

This amendment addresses the following revision requested by regulatory authority:

- To revise exclusion criteria to exclude patients receiving systemic corticosteroids at dose of >10mg/day prednisone
- To specify in more detail guidelines and criteria about immune related and non- immune related AE management and study treatment recommendations
- To clarify the criterion that patients beyond initial RECIST v1.1 defined disease progression are allowed to continue study treatment
- To specify more frequent evaluations may be performed at investigator's discretion or if recommended by drug product information.

Minor changes have been made for consistency and to operations- related specifications.

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 criteria

- Revised Exclusion criterion 9 to exclude patients who receive >10mg/per day prednisone

Section 6.2 Dose modifications (patients in PDR001 arm) has been renamed as "Safety and Dose modifications (patients in PDR001 arm)"

- Section 6.2.2.1 Anticipated risks and safety concerns of the study drug (patients in PDR001 arm) has been moved to Section 6.2.1
- Section 6.2.2.2 Immune-related Adverse Events (irAEs) has been moved to Section 6.2.2
- Section 6.2.1 Dose modifications and dose delay has been moved to Section 6.2.3
- Section 6.2.2 Management of toxicities has been renamed as "Management of toxicities and immune related AEs (irAEs) " and moved to Section 6.2.4
- Updated Table 6-2 Criteria for interruption, delay and discontinuation of PDR001

Section 7.1 Study flow and visit schedule

- Table 7-2 Added footnote "More frequent evaluations may be performed at the investigator's discretion if medically indicated or if recommended by drug product information."
- Table 7-1; 7-2; 7-3 modified to be consistent that first dose of C1D1 should be implemented within 72 hours after randomization.

Section 7.1.2 Treatment Period

- Defined the criteria for continuing treatment beyond initial RECISTv1.1, defined disease progression.

Section 14.4 Appendix 4 Management Algorithms

- Added algorithms for managing the following groups of AEs: Gastrointestinal; Renal; Pulmonary; Hepatic; Endocrinopathy; Skin and Neurological.

IRB/IEC/HA

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

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

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

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Nasopharyngeal cancer (NPC) is a squamous carcinoma that usually develops around the ostium of the Eustachian tube in the lateral wall of the nasopharynx. Rare amongst whites, NPC is endemic (up to 50:100,000) in South East Asia, North Africa, Middle East and the Artic (Bray et al 2008). Chinese emigrants continue to have a high incidence of the disease, but the rate of NPC amongst ethnic Chinese born in North America is considerably lower (around 10:100,000) than those born in China.

The etiology is complex and includes genetic, environmental and viral components. Epstein-Barr Virus (EBV) has been associated with NPC as NPC tumor cells express EBV proteins such as EBNA-1 and LMP1 and 2 (Chien et al 2001).

The World Health Organization (WHO) classifies NPC in 3 main subtypes. Type 1 is a well differentiated keratinizing squamous carcinoma. Type 2 is non-keratinizing moderately-differentiated, and type 3 is non-keratinizing and undifferentiated, accounting for 90% of the tumors. Type 2 and 3 are Epstein - Barr Virus (EBV) associated, and this makes NPC unique from other cancers of the head and neck.

More than 50% of the patients present at the time of diagnosis with locally advanced disease (stage III to IVB, according to the American Joint Committee of Cancer AJCC 13th Edition). NPC is characterized by an inherent chemosensitive and radiosensitive biology, and the spectrum of chemotherapeutics that can be used is fairly wide. The standard treatment for loco-regionally advanced NPC is platinum-based chemoradiotherapy (CRT), which has shown to confer survival benefit, over radiotherapy alone in 8 randomized trials (Ma et al 2008, Kam et al 2007, Chan et al 2005). Despite the initial response rate as high as 65-70%, up to 40% of the patients relapse with distant metastases. The 5-year survival rates for locally advanced recurrent and metastatic disease are only 55% and 38%, respectively. The salvage therapy includes gemcitabine, capecitabine or taxanes, but none of these are approved for the treatment of NPC. The median progression free survival (mPFS) for patients who had at least one line of treatment ranges from 3.9 to 5.1 months and the median overall survival (mOS) is approximately 12-13 months.

Treatment of locally advanced recurrent and metastatic NPC remains an unmet need in the developing world.

1.2 Overview of conventional therapy in NPC

Platinum combination regimens are commonly used in first-line for metastatic or recurrent NPC patients, since cisplatin represents the most effective drug. Patients who progress on a first-line treatment have a poor prognosis and are treated with palliative chemotherapy, as there are no standard regimens. Active agents used in second line (Table 1-1) include paclitaxel, docetaxel, gemcitabine, capecitabine, irinotecan, vinorelbine, ifosfamide, doxorubicin and oxaliplatin, which can be used as single agents or in combination. It has to be stressed, however, that whatever the treatment applied in second line, the prognosis remains poor, with a short median

time to progression (mTTP) and the median overall survival (mOS) usually does not exceed 13 months (Table 1-1).

Table 1-1 Second line treatment in metastatic or recurrent NPC

Source, n=sample size	Regimen	Median TTP (mo)	Median OS (mo)
Chua (2000), n=19	Ifosfamide, 5-FU, leucovorin	6.5	NR
Airoldi (2002), n=12	Carboplatin-Paclitaxel	-	9.5
Foo (2002), n=27	Gemcitabine	5.1	7.2
Chua (2003), n=17	Capecitabine	4.9	7.6
Poon (2005), n=28	Irinotecan	-	11.4
Wang (2006), n=39	Gemcitabine-Vinorelbine	-	11.9
Zhang (2008), n=32	Gemcitabine	5.1	16
Ngeow (2011), n=30	Docetaxel (weekly)	5.3	12.8
Zhang (2012), n=35	Pemetrexed	1.5	13.3
Yau (2012), n=15	Cisplatin-Pemetrexed	7.5	Not reported
Peng (2013), n=48	Nedaplatin-Capecitabine	5.8	12.4

Source: courtesy of Dr Brigette Ma, unpublished.

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

1.3.1 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 cell (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 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 numbers of Tregs at the tumor site (Wang 2009, Mangsbo 2010, Mkrtichyan 2011, Rosenblatt 2011).

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) with an acceptable and manageable safety profile (Topalian 2012, Hamid 2013, Topalian 2014, Lyford-Pike 2013).

PDR001 is a high-affinity, ligand-blocking, humanized anti-PD-1 IgG4 antibody which blocks the binding of PD-L1 and PD-L2 to PD-1. This antibody does not induce antibody-dependent cell-mediated cytotoxicity (ADCC).

1.3.1.1 PDR001 non-clinical experience

PDR001 binds specifically and with high affinity to human PD-1.

PDR001 does not cross-react with rodent PD-1, and cannot be evaluated in murine tumor models. It does cross-react with cynomolgus monkey PD-1, and is functionally active, making cynomolgus monkey a relevant species for toxicology studies.

Biacore binding studies for PDR001 have shown an equilibrium dissociation constant (K_D) of 0.827 ± 0.505 nM for Human PD-1 and 0.929 ± 0.150 nM for Cynomolgus monkey.

PDR001 was able to inhibit the binding of PD-L1 and PD-L2 to PD-1 with an IC50 of 0.94 ± 0.15 nM and 1.3 ± 0.25 nM, respectively.

PDR001 shows functional activity in vitro/ex vivo. In ex vivo lymphocyte stimulation assays using human blood, PDR001 enhances IL-2 production by approximately 2 fold, in response to super antigen stimulation with Staphylococcal enterotoxin B (SEB).

The activity of PDR001 was also tested in an *in vitro* Mixed Lymphocyte Reaction (MLR) assay based on the co-culture of PD-L1+ monocyte-derived DCs with allogeneic CD4+ T cells. Both cell proliferation and IFN-γ release were measured as readouts for this functional assay. Addition of PDR001 resulted in a less than 2-fold increase in proliferation over isotype control. However, PDR001 led to a dose dependent increase in IFN-γ release by an average factor of 8-13 times the levels observed with an isotype control antibody at doses ranging between 5μg/ml and 25μg/ml. For further details, please refer to the [PDR001 Investigator's Brochure].

1.3.1.2 PDR001 clinical experience

PDR001 is evaluated in a first-in-human, multi-center, open-label study [CPDR001X2101] 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 for RP2D. 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.

The study is ongoing in Phase II part. For further details, please refer to the [PDR001 Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

NPC is an inflammatory cancer associated with EBV infection (Chung et al 2013). A characteristic feature of NPC is the presence of immune infiltration in the primary tumor consisting of T cells, B cells, monocytes and dendritic cells. In NPC there is evidence for functional inactivation of NPC primary tumor infiltrating lymphocytes (TIL) as these, in contrast to peripheral T cells, have an "exhausted" phenotype and fail to produce IFN-γ upon stimulation (Li et al 2007, Ott et al 2013). Recently, PD-1 expression on CD8+ T cells from NPC tumors was found to be upregulated compared to CD8+ T cells from control nasopharyngeal tissues (Hsu et al 2010). Higher PD-1 expression was associated with shorter overall survival (OS), disease-free survival (DFS) and was also an independent risk factor for death and treatment failure.

Preliminary data from the early clinical studies of anti PD-1 antibodies nivolumab and pembrolizumab, as well as the anti-PD-L1 antibodies MPDL3280A and MEDI4736, suggested that PD-L1 protein expression on tumor cells might associate with clinical response to these agents (Topalian 2012, Weber 2013, Taube 2014, Bellmunt 2014, Creelan 2014). More recent studies have confirmed that the association of tumor-infiltrating immune cell PD-L1 expression with treatment response appeared stronger than that with tumor cell PD-L1 expression (Herbst et al 2014).

Furthermore, high levels of PD-L1 in tumor infiltrating immune cells may identify patients who respond to checkpoint inhibitors, as complete response following PD-1 blocking antibodies has also been observed in patients who were PD-L1 negative in tumor cells (Herbst et al 2014).

We examined 115 primary NPC tumors for expression of PD-L1 and CD8, and found that the large majority (89.5%) expresses both high levels of PD-L1 and CD8, confirming both the target expression as well as a rich tumor immune infiltration [RDS-2015-00010].

Recent study also found that EBV-induced latent membrane protein 1 (LMP1) and IFN-γ pathways cooperate to regulate PD-L1 in NPC cell lines through STAT3, AP-1, and NF-κB pathways. PD-L1 overexpression in the tumor sample was associated with worse disease-free survival in NPC patients (Fang et al 2014, Zhang et al 2015).

For these reasons, it is rational to hypothesize that treatment with a PD-1 blocking antibody may break tumor- induced immune suppression and produce clinical benefit in a proportion of NPC patients who have a worse prognosis.

2.2 Rationale for the study design

This is an open-label, multi-center, randomized and controlled phase II study of single-agent PDR001 in patients with moderately differentiated/undifferentiated, locally advanced recurrent or metastatic NPC, who have progressed on or after first-line platinum-based therapy.

A randomized controlled study with PFS as primary endpoint is considered the appropriate study design to assess clinical activity of PDR001, given the high percentage of response to salvage chemotherapy, ranging up to 30%. This response is however of short duration, and TTP /PFS is around 5-6 months at best. It is therefore difficult to assess clinical activity of PDR001 in NPC without a control arm, and response rate (RR) may be a misleading endpoint.

Eligible patients who have progressed on platinum-based first-line therapy will be randomized 2:1 to either PDR001 administered i.v. every 4 weeks (Q4W) or an investigator's choice of chemotherapy.

The primary endpoint will be progression free survival (PFS) as per RECIST v1.1, based on an independent central reader, to assess the efficacy of PDR001 versus investigator's choice of chemotherapy. Disease progression will be evaluated according to investigator and independent central review. The local investigator's assessment will be used for treatment decision making (study discontinuation due to progressive disease (PD) as per immune-related response criteria (irRC)). Secondary endpoints include immune-related Progression Free Survival (irPFS), duration of response (DOR), overall response rate (ORR), time to progression (TTP), overall survival (OS), and safety. A biomarker evaluation will also be performed (please refer to Section 2.5).

If the study meets its primary endpoint, it will demonstrate the ability of PDR001 to elicit an anti-tumor response and improved treatment benefit versus commonly used chemotherapy agents in the second-line treatment of locally advanced recurrent or metastatic NPC patients who have progressed on or after first-line platinum-based therapy, establish a Phase II proof-of-concept study, and open the path for a novel standard of care regimen for this patient population.

2.3 Rationale for dose and regimen selection

The dose and regimen which will be used in this study is the recommended phase II dose (RP2D) established in the [CPDR001X2101] phase I (first-in-human) study. After completion of the dose escalation and review of the data, the RP2D was declared as 400 mg Q4W.

2.4 Rationale for choice of comparator drugs

There is no gold standard for locally advanced recurrent or metastatic NPC patients who progress on or after the platinum-based first-line therapy. The choice of chemotherapy following progression on or after first-line therapy for metastatic NPC is not well defined and is based on several factors, including previous chemotherapy exposure, performance status, comorbidity conditions and tumor characteristics. None of the chemotherapeutic agents that are currently used as palliative treatment in these patients have been approved specifically for use in this setting. The rationale for giving the investigator a choice of active comparator regimen

is to allow the investigator to select the most suitable option for the patient, according to the institutional guidelines.

2.5 Rationale for use of blood and tumor tissue biomarkers

Emerging data demonstrates a correlation between the presence of PD-L1 surface expression on tumor cells and tumor infiltrating immune cells and clinical efficacy of checkpoint inhibitors (anti-PD-1 /PD-L1 therapies) (Herbst et al 2014, Tumeh et al 2014 and Powles et al 2014). Similarly, the presence of pre-existing exhausted tumor infiltrating lymphocytes (TIL) is associated with response to anti PD-L1/PD-1 treatment whilst immunological ignorance is associated with absence of clinical response (Herbst et al 2014 and Tumeh et al 2014).

In the periphery, circulating increases of CD8+, Ki67+, T cells, IFN-γ, IL-18 and CXCL11 (IFN-γ induced CCK) suggest the rapid expansion of a pre-existing primed immune response, whilst the decrease of IL-6 is indicative of a reduction of Myeloid-derived Suppressor Cell (MDSC) (Herbst et al 2014, Tumeh et al 2014 and Powles et al 2014).

Understanding the biology of the tumor microenvironment in tumor samples pre- and post-treatment is critical to evaluate the role of PDR001 in NPC patients. Furthermore, since PD-L1 is not the only mechanism that allows tumor escape, it is important to assess the expression of other well identified checkpoint inhibitors such as LAG-3 and TIM-3 in tumor samples.

Biomarkers in peripheral blood include immunophenotype and quantification of soluble proteins and expression of immune related genes.

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 10.4.
To assess the efficacy of PDR001 versus investigator's choice of chemotherapy in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic NPC who progressed on or after first-line therapy	Progression free survival (PFS) as per RECIST v1.1 (Appendix 1) using central assessment	
Secondary		Refer to Section 10.5.
To evaluate the anti-tumor activity of PDR001 versus investigator 'choice of chemotherapy in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic NPC who progressed on or after first-line therapy	Overall survival (OS), overall response rate (ORR), duration of response (DOR), time to progression (TTP) and immune related progression free survival (irPFS) as per irRC (Appendix 2) using central assessment	
To characterize the safety and tolerability of PDR001	Safety: Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including changes in laboratory parameters, vital signs and electrocardiograms (ECGs)	
To characterize the pharmacokinetic profile of PDR001 (patients in PDR001 arm)	Serum PK parameters (e.g. AUC, Cmax, Tmax, half-life); Serum concentration vs. time profiles	
To assess emergence of anti-PDR001 antibodies following one or more intravenous (i.v.) infusions of PDR001(patients in PDR001 arm)	Presence and/or concentration of anti-PDR001 antibodies	
To assess potential predictive markers of efficacy of PDR001 in tumor sample (patients in PDR001 arm)	Assess potential associations between expression of PD-L1, CD8,Foxp3 and other immunological markers such as Lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin domain and mucin domain-3 (TIM-3), with anti-tumor activity	

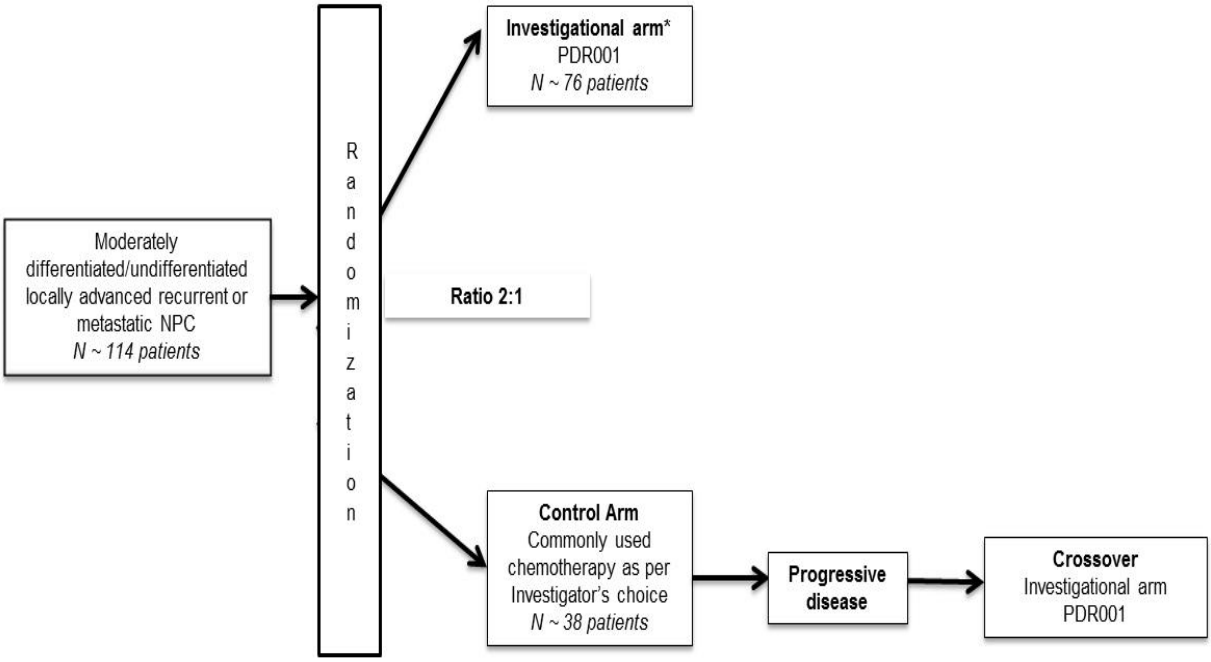
Objective	Endpoint	Analysis
To assess the pharmacodynamic effect of PDR001 in tumor sample (patients in PDR001 arm)	TIL counts and expression of immune-related genes (RNA/protein in tumor sample)	
To assess the pharmacodynamic effect of PDR001 in peripheral blood (patients in PDR001 arm)	Assess peripheral, soluble ligands and cytokine levels (including but not limited to IFN-γ, TNF-α, IL-6)	
[redacted]		

4 Study design

4.1 Description of study design

This is an open-label, multi-center, randomized, controlled phase II study to evaluate the efficacy and safety of PDR001 versus investigator's choice of treatment in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic NPC who progressed on or after first-line treatment. The study design is summarized in Figure 4-1.

Figure 4-1 Study design



*Patients treated with PDR001 will continue treatment until confirmed PD as per irRC. Please refer to Section 7.1.2 for further details.

Approximately 114 patients will be recruited and randomized in the study in order to observe 70 events of disease progression for the primary endpoint PFS analysis. The randomization will be stratified by disease status (locally advanced recurrent NPC vs. metastatic NPC). Please refer to Section 10 for details of analysis and reporting of data.

Patients in the control arm will be allowed to crossover to PDR001 treatment if they have radiological progression (per RECIST v1.1) documented by an independent central review and the investigator believes this is the best treatment option for the patient. Each case must be first discussed with Novartis. Any patient enrolled in the control arm who does not meet the criteria of radiologically assessed disease progression will not be eligible for crossover to PDR001 arm. Please refer to Section 7.1.2.1 for further details.

This study will use an Interactive Response Technology (IRT) system for randomization and for study management of PDR001 study drug (see Section 6.4). Eligible patients should receive the first dose of study treatment within 28 days of signing the study informed consent.

The study is comprised of 3 periods: Screening/Baseline, Treatment, Follow-up period (30-day Safety for Chemotherapy arm and 150-day Safety for PDR001 arm and crossover arm, Disease Progression and Survival). Please refer to Section 7 for detailed information on assessments to be performed during each period.

4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned.

4.3 Definition of end of the study

End of study will be defined as the time when:

- the last randomized patient has died, has been lost to follow-up, withdrawn consent, or completed his/her final study visit,

or

- 24 months survival follow-up after the first dose of the last randomized patient,

or

- the date when the study is terminated early,

or

- another clinical study becomes available that can continue to provide study treatment in this patient population, and all patients ongoing are transferred to that clinical study,

whichever occurs first. Please refer to Section 7.1.3 for details.

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.

See Section 10 Statistical Methods and Data Analysis for details of timing of the primary analysis.

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 should be performed as described in Section 7.1.3 for a discontinued 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

The study will be conducted in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic NPC who progressed on or after first-line platinum-based therapy.

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

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.
2. Age ≥ 18 years.
3. Histologically documented non-keratinizing locally advanced recurrent or metastatic NPC.
4. Must be resistant to platinum-based chemotherapy (defined as progression on or after platinum-based chemotherapy given in the recurrent/metastatic setting).
5. May have received at least 1 prior therapy for recurrent or metastatic disease, up to 2 prior systemic therapies.
6. ECOG Performance Status ≤ 2.
7. An archival tumor specimen or newly obtained tumor sample may be submitted at screening/baseline (a new tumor sample is preferred), unless agreed differently between Novartis and the Investigator.
8. At least 1 measurable lesion (as per RECIST v1.1) progressing or new since last anti-tumor therapy. Lesions in previously irradiated areas should not be considered measureable unless there is clear evidence of progression in such lesions since the radiotherapy.
9. Prior treated brain or meningeal metastases must be without MRI evidence of progression for at least 8 weeks and off systemic steroids for at least 2 weeks prior to screening/baseline. Lesions extending to the base of skull or abutting the temporal lobes are included.
10. Must be willing to undergo testing for human immunodeficiency virus (HIV) if not tested within the past 6 months. If HIV+ positive, patient will be eligible for study provided that his/her CD4+ count ≥ 300/μL; his/her viral load is undetectable; he/she is currently receiving highly active antiretroviral therapy (HAART).
11. Life expectancy > 12 weeks.

5.3 Exclusion criteria

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

1. History of severe hypersensitivity reactions to other monoclonal Antibodies (mAbs).

2. Having out of range laboratory values defined as:
   - Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 40 mL/min
   - Total bilirubin > 1.5 x ULN, 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) > 3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if ALT > 5 x ULN
   - Aspartate aminotransferase (AST) > 3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if AST > 5 x ULN
   - Absolute neutrophil count (ANC) < 1.5 x 10^9/L
   - Platelet count < 75 x 10^9/L
   - Hemoglobin < 9 g/dL
3. Active autoimmune disease or a documented history of autoimmune disease, or any condition that requires systemic steroids, except vitiligo or resolved asthma/atopy that is treated with broncho-dilators (e.g. albuterol).
4. Active HBV and HCV infections requiring therapy. Patients on antiviral therapy may be allowed if disease is controlled according to local treatment standard.
5. 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.
6. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results.
7. Systemic anti-cancer therapy within 2 weeks of the first dose of study treatment, unless agreed otherwise with Novartis. Any patient with the following reported drug-related adverse events on anti-CTLA4 will not be permitted on study: hepatic, diarrhea/colitis or endocrine adverse events (AE)s Grade ≥ 2, any other non-laboratory immune-related AE ≥ Grade 3. Patients must have minimum 8 week washout period between the last dose of anti-CTLA4 and the first dose of PDR001.
8. Prior PD-1- or PD-L1-directed therapy.
9. Receiving treatment with systemic steroid therapy or any immunosuppressive therapy, other than replacement-dose steroids<10mg/day prednisone in the setting of adrenal insufficiency. Topical, inhaled, nasal and ophthalmic steroids are not prohibited.
10. Use of any vaccines against infectious diseases (e.g. varicella, pneumococcus) or investigational therapeutic cancer vaccines within 4 weeks of initiation of study treatment.
11. 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).
12. Radiotherapy within 2 weeks of the first dose of study treatment, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass.

13. Participation in an interventional, investigational study within 2 weeks of the first dose of study treatment, unless agreed otherwise with Novartis.
14. Presence of ≥ CTCAE grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if ≥ CTCAE grade 3) due to prior cancer therapy, unless agreed otherwise with Novartis.
15. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) ≤2 weeks prior to start of 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.
16. 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.
17. 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. 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 6 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 of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

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) or tubal ligation at least 6 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.

18. Sexually active males unless they use a condom during intercourse while taking drug and for 150 days after stopping study treatment 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.
19. Patient with contraindications for the chosen treatment (control arm only)

6 Treatment

6.1 Study treatment

The study treatment in this study refers to:

- **Investigational drug**: PDR001
  or
- **Chemotherapy**: as per investigator's choice (except for re-challenge with previously used drugs)

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
PDR001	Powder for solution for infusion	400mg	Every 4 weeks (Q4W)
Commonly used chemotherapy as per investigator's choice	As described in the drug label	As described in the drug label	As described in the drug label

PDR001 will be administered via i.v. infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 4 weeks. Next dose may be delayed by up to 7 days to recover from previous AEs. If the next dose cannot be administered within the above mentioned 7-days delay, then the dose should be skipped. Dosing will resume at the scheduled dose and assessment schedule will be shifted accordingly.

6.1.2 Treatment duration

All patients treated with either PDR001 or chemotherapy (per Investigator's choice) will begin treatment on Cycle 1 Day 1. Each cycle will have 28 days if treated with PDR001. Patients may be discontinued from study treatment earlier due to unacceptable toxicities, confirmed disease progression (per irRC only for patients treated with PDR001) and/or treatment is discontinued at the discretion of the investigator or the patient. Patients who discontinue study treatment should not be considered discontinued from the study (please refer to Section 7.1.3 and Section 4.3 for further details).

6.1.3 Ancillary treatments (patients in PDR001 arm)

All patients randomized into the PDR001 arm, 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 may only continue on the study following discussion with Novartis.

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 Table 6-2.

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.

6.1.4 Chemotherapy treatments (patients in control arm only)

For patients randomized into the control arm, investigators should follow local guidelines as per standard of care and approved product labels especially regarding pre-medication schemes, the contraindications, the contraceptive regimens, the dosage adjustment in case of toxicity, the patient monitoring and the prohibited or used with caution drug.

6.2 Safety and dose modifications (patients in PDR001 arm)

6.2.1 Anticipated risks and safety concerns of the study drug (patients in PDR001 arm)

Appropriate eligibility criteria as well as specific dose modification 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 Table 6-2. Refer to preclinical toxicity data provided in the [PDR001 Investigator's Brochure].

6.2.2 Immune-related adverse events (irAEs)

The emergence of immune related AE (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 to verify the immune related nature of the AE, and exclude the neoplastic, infectious or metabolic origin of the AE.

6.2.3 Dose modifications and dose delay

There will be no dose modifications allowed for PDR001.

All dose interruption, delay and discontinuation should be based on the worst preceding toxicity (CTCAE Version v4.03). If a patient experiences a Grade 3 PDR001-related AE, treatment with PDR001 should be interrupted unless otherwise specified in Table 6-2 Refer to Section 6.2 for Management of toxicities and immune related AEs. Following resolution of the toxicity to

Grade 1, patient may resume PDR001 treatment at the same dose level, if there is no evidence of disease progression.

A decision to resume treatment with PDR001 following the occurrence of a Grade 3 AE 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.

If a patient experiences any Grade 4 PDR001-related AE, the treatment should be discontinued unless otherwise specified in Table 6-2.

In case the infusion cannot be administered at the scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days the procedures at the original schedule visit should be performed. If the delay is longer than 7 days, the procedure of the following visit should be performed.

Patients who missed 2 infusions plus 7 days should be discontinued from the study treatment and enter the Follow-up period. Exceptions may be made on a case by case basis after discussion between Novartis and the Investigator.

Patients who discontinue the study for an AE or clinically significant abnormal laboratory value must be followed as described in Section 6.2.

All changes in study drug administration must be recorded on the Dose Administration Record eCRF.

6.2.4 Management of toxicities and immune related AEs (irAEs)

All the patients whose treatment is interrupted or permanently discontinued due to an 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 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. In case of suspected irAEs, the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed.

Algorithms have been provided to assist investigators in assessing and managing the following groups of irAEs: Gastrointestinal; Renal; Pulmonary; Hepatic; Endocrinopathy; Skin; and Neurological. Management Algorithms can be found in the Appendix 4.

For non- immune related AE as Grade 1 or 2, treatment with PDR001 maintains dose and schedule unless it specifies in the Table 6-2.

Table 6-2 Criteria for interruption, delay, re-initiation and discontinuation of PDR001

Worst toxicity CTCAE Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for PDR001 during a cycle of treatment**
Infusion Reaction or Hypersensitivity reaction	
Grade 1	Decrease infusion rate until recovery of the symptoms
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 study.
Grade 3 or Grade 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.
Neutropenia (ANC)	
Grade 3 (ANC < 1000 - 500/mm^3)	Dose delay for PDR001-related Grade 3 until resolved to ≤ Grade 1
Grade 4 (ANC < 500/mm^3)	Discontinue for PDR001-related Grade 4 > 7 days duration
Thrombocytopenia	
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Dose delay for PDR001-related Grade 3 until resolved to ≤ Grade 1 Discontinue for PDR001-related Grade 3 > 7 days or associated with bleeding
Grade 4 (PLT < 25,000/mm^3)	Discontinue for PDR001-related Grade 4
Febrile neutropenia	
(ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Dose delay for PDR001-related Grade 3 until resolved to ≤ Grade 1 Discontinue for PDR001-related Grade 4

Worst toxicity CTCAE Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for PDR001 during a cycle of treatment**
Lymphopenia	
Grade 3 (<0.5-0.2 x 10^9/L)	Maintain dose and schedule for PDR001-related ≤ Grade 3
Grade 4 (<0.2 x 10^9 /L)	Dose delay for PDR001-related Grade 4 until resolved to ≤ Grade 3 PDR001-related Grade 4 lymphopenia or leukopenia does not require discontinuation
Renal See Appendix 4 "Renal Adverse Event Management Algorithm" for additional guidance on monitoring and management of any grade events	
Serum creatinine	
Grade 2 (> 1.5 - 3.0 x ULN) or Grade 3 (> 3.0 - 6.0 x ULN)	Dose delay for PDR001-related ≥ Grade 2 until resolved to ≤ Grade 1
Grade 4 (> 6.0 x ULN)	Discontinue for PDR001-related Grade 4
Liver See Appendix 4 "Hepatic Adverse Event Management Algorithm" for additional guidance on monitoring and management of any grade events	
AST or ALT	
Grade 2 (> 3.0 - 5.0 x ULN)	Dose delay for PDR001-related ≥ Grade 2 until resolved to ≤ Grade 1 Discontinue for concurrent AST or ALT >3x ULN and total bilirubin > 2x ULN
Grade 3 (> 5.0 - 20.0 x ULN) or Grade 4 (> 20.0 x ULN)	Discontinue for PDR001-related ≥ Grade 3 or Grade 4
Bilirubin*	
Grade 2 (> 1.5 - 3.0 x ULN)	Dose delay for PDR001-related ≥ Grade 2 until resolved to ≤ Grade 1 Baseline total bilirubin is within normal limits, delay dosing for PDR001-related Grade ≥ 2 toxicity Baseline AST/ALT or total bilirubin in the Grade 1 toxicity requiring dose delays for reasons other than a 2-Grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin
Grade 3 (> 3.0 - 10.0 x ULN) or Grade 4 (> 10.0 x ULN)	Discontinue for PDR001-related ≥ Grade 3 or Grade 4
Asymptomatic amylase and/or lipase elevation**	
Grade 3 (> 2.0 - 5.0 x ULN) or Grade 4 (> 5.0 x ULN)	Any Grade ≥3 PDR001-related isolated amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay or discontinuation. The Novartis Medical Monitor should be consulted for such amylase or lipase abnormalities

Worst toxicity CTCAE Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for PDR001 during a cycle of treatment**
Cardiac general	
Grade 2 or Grade 3	Dose delay for PDR001-related ≥ Grade 2 until resolved ≤ Grade 1 Discontinue for PDR001-related Grade 3 lasting > 7 days
Grade 4	Discontinue for PDR001- related Grade 4
Endocrine See Appendix 4 "Endocrinopathy Management Algorithm" for additional guidance on monitoring and management of any grade events	
Grade 2 or Grade 3	Dose delay for any Grade ≥ 2 PDR001-related until resolved ≤ Grade 1 Grade 3 PDR001-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
Grade 4	Grade 4 PDR001-related endocrinopathies, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Novartis Medical Monitor.
Skin Rash/photosensitivity See Appendix 4 "Skin Adverse Event Management Algorithm" for additional guidance on monitoring and management of any grade events.	
Grade 2	In presence of Grade 2 PDR001-related skin toxicity, treatment may be resumed (even if patient experience before a Grade 3 PDR001-related toxicity)
Grade 3 or Grade 4	Dose delay for PDR001-related Grade 3 until resolved ≤ Grade 1 Discontinue for PDR001-related Grade 3 lasting > 7 days, or PDR001-related Grade 4
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	
Any Grade	Permanently discontinue study treatment.
Gastrointestinal See Appendix 4 "GI Adverse Event Management Algorithm" for additional guidance on monitoring and management of any grade events	
Diarrhea* **	
Grade 2	Dose delay for PDR001-related Grade ≥ 2 until resolved ≤ Grade 1 or baseline
Grade 3 or Grade 4	Discontinue for any PDR001-related Grade 3 lasting > 7 days, or PDR001-related Grade 4
Fatigue/Asthenia Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 3 or Grade 4	Dose delay for PDR001-related Grade 3 until resolved ≤ Grade 1 Discontinue for PDR001-related Grade 3 lasting > 7 days, or PDR001-related Grade 4
Any Neurological toxicity See Appendix 4 "Neurological Adverse Event Management Algorithm" for additional guidance on monitoring and management of any grade events	
Grade 2	Dose delay for PDR001-related Grade ≥ 2 until resolved ≤ Grade 1

Worst toxicity CTCAE Grade (unless otherwise specified)	**Recommended dose interruption, delay and discontinuation for PDR001 during a cycle of treatment**
Grade 3 or 4	Discontinue for PDR001-related Grade 3 lasting > 7 days, or PDR001-related G4
Ocular (uveitis, eye pain, blurred vision)	
Grade 2	Dose delay for PDR001-related Grade ≥ 2 until resolved ≤ Grade 1 Discontinue for any Grade 2 PDR001-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
Grade 3 or Grade 4	Discontinue for Grade 3 PDR001-related uveitis of any duration Discontinue for PDR001-related Grade 3 lasting > 7 days, or PDR001-related Grade 4
Pulmonary (pneumonitis, bronchospasm) See Appendix 4 “Pulmonary Adverse Event Management Algorithm” for additional guidance on monitoring and management of any grade events.	
Grade 1	Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by Novartis Medical Monitor.
Grade 2	Dose delay for PDR001-related Grade ≥ 2 until resolved ≤ Grade 1
Grade 3 or Grade 4	Discontinuation for Grade 3 PDR001-related pneumonitis of any duration Discontinue for PDR001-related Grade 3 lasting > 7 days or PDR001-related Grade 4
Cytokine Release Syndrome (CRS)	
Grade 2 or Grade 3 or Grade 4	If CRS is suspected (very high fever and precipitous drops in blood pressure, myalgia, change in mental status) treat with corticosteroids.
Other Non-laboratory adverse events	
Grade 2	Dose delay for PDR001-related Grade ≥ 2 until resolved ≤ Grade 1
Grade 3 or Grade 4	Discontinue for PDR001-related Grade 3 lasting > 7 days, or PDR001-related Grade 4
Other laboratory adverse events	
Grade 3 or Grade 4	Dose delay for PDR001-related ≥ Grade 3 until resolved to ≤ Grade 1 Isolated Grade 4 electrolyte imbalances/abnormalities not associated with clinical sequelae and corrected with supplementation/appropriate management within 72hrs of their onset do not require discontinuation.
*Note: If Grade 3 or 4 hyper-bilirubinemia 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 delay treatment until resolved ≤ Grade 1 and continue treatment at the discretion of the investigator. **Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur for a second time, patients will be discontinued permanently from study treatment. ***Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.	

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed.

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 during the study 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 during screening/baseline.

6.3.2 Permitted concomitant therapy requiring caution and/or action (patients in PDR001 arm)

Treatment with hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) may not be taken during the study. If a patient is using erythropoiesis 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 International Normalized Ratio (INR) should be monitored as clinically indicated per investigator's discretion. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor sample 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.

A brief (< 24 hours) course of steroids for prophylaxis against contrast dye allergy is permitted for patients undergoing tumor assessments with exposure to the allergen.

6.3.3 Prohibited concomitant therapy (patients in PDR001 arm)

During the course of the study, patients may 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, with the only exclusion of steroids for the treatment of PDR001 infusion reaction, irAEs, replacement-dose steroids in the setting of adrenal insufficiency (providing this is ≤ 10 mg/day prednisone or equivalent), or transient exacerbations of other underlying diseases such as chronic obstructive pulmonary disease (COPD) requiring treatment for < 3 weeks. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at non-immunosuppresive doses (≤ 10 mg/day of prednisone or equivalent) before the next study

drug administration. If more than 10 mg/day prednisone is used, PDR001 treatment should be suspended (see Section 6.2.4).

Topical, inhaled, nasal and ophthalmic steroids are not prohibited. The use of live vaccines is not allowed through the whole duration of the study. Other vaccines are excluded, except inactivated seasonal influenza vaccines.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening/baseline and 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 Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available to the investigator through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Patient No. must not be reused for any other Patient and the Patient No. for that individual must not be changed. If the patient is randomized but fails to start treatment for any reason, the reason will be entered into the End of Treatment phase Disposition eCRF and IRT must be notified within 2 days that the patient was not treated.

6.4.2 Treatment assignment or randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms (Section 4.1 and Section 6.1) in a ratio of 2:1. Randomization will be stratified by patient's baseline disease status: locally advanced recurrent NPC vs. metastatic NPC (Section 4.1). The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT 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. The randomization number will not be communicated to the caller.

For the patients crossing over to PDR001 arm, and only after agreement with Novartis, the investigator or his/her designee will call or log on to the IRT and confirm that the patient fulfills

the criteria to crossover. The IRT will assign a unique medication number for the study drug to be administered to the patient.

6.5 Study drug preparation and dispensation

PDR001

PDR001 (100 mg powder for solution for infusion) will be administered intravenously as a 30 minute infusion (up to 2 hour, if clinically indicated). Further instructions for the preparation and dispensation of PDR001 are described in the [Pharmacy Manual].

Chemotherapy

Commercially available chemotherapy will be sourced locally by each study site. Generic chemotherapy may be used for study treatment.

All dosages for PDR001 and for the chemotherapy prescribed to the patient and all dose changes (except for PDR001 as no dose modifications) during the study must be recorded on the respective Dosage Administration Record eCRF.

6.5.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and a specific visit. Responsible site personnel will identify the study treatment package(s) to administer to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

PDR001 (100 mg powder for solution for infusion) will be supplied by Novartis to Investigator as open label medication.

6.5.2 Drug supply and storage

PDR001

PDR001 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, PDR001 should be stored according to the instructions specified on the drug labels.

Chemotherapy

Chemotherapy should be stored and prepared according to the instructions on the package insert or summary of product characteristics of the commercial supply. The preparation and disposal of chemotherapy must be in accordance with local institutional guidelines.

6.5.3 Study drug compliance and accountability

6.5.3.1 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.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatments (PDR001 and chemotherapy) 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.

6.5.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1, Table 7-2 and Table 7-3 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/Baseline evaluations must be performed ≤ 28 days of Cycle 1 Day 1 (except for the pregnancy test which has to be performed within 72 hours before first dose). Assessments performed as part of the screening/baseline evaluations and within 3 days prior to the first dose of study treatment, are not required to be repeated on Cycle 1 Day 1. Laboratory and radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within the screening/baseline time window.

For the patients in the crossover, the first dose of PDR001 on Cycle 1 Day 1 should be administered ≤ 21 days from the radiological assessment performed as part of the End of Treatment (EoT1) visit. Assessments performed as part of the EoT1 visit and within 3 days prior to the first dose of PDR001, are not required to be repeated on Cycle 1 Day 1.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of +/- 7 days is allowed. If the infusion of PDR001 is delayed, the assessments will be shifted accordingly. On PK collection days the windows are provided in Section 7.2.3.

Table 7-1 Visit evaluation schedule (patients in PDR001 arm)

Visit name	Category	Protocol Section	Screening/ Baseline Period	Treatment Period													Follow-up Period[10]		
			Screening/ Baseline	Cycle 1				Cycle 2			Cycle 3				Subsequent cycles	EoT1	150 - Day Safety[6]	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**8**	**15**	**1**				
Obtain Informed Consent	D	7.1.1.	X																
IVRS/IRT Registration	D	6.4.	X[1]																
Demography	D	7.1.1.2.	X																
Inclusion/ exclusion criteria	D	5.2/5.3.	X																
Newly obtained or archival tumor sample	D	7.2.4.	X																
Medical History	D	7.1.1.2.	X																
Diagnosis and extent of cancer	D	7.1.1.2.	X																
Prior antineoplastic therapy	D	6.3.1.	X																
Prior/concomitant medications	D	6.3.1.	X	Continuous															
Physical exam	S	7.2.2.1.	X	X			X	X		X	X			X	X[2]	X			
Vital signs	D	7.2.2.2.	X	X			X	X		X	X			X	X[2]	X			
Height	D	7.2.2.3.	X																
Weight	D	7.2.2.3.	X	X				X			X				X[2]	X			
ECOG Performance status	D	7.2.2.4.	X	X							X				X[2]	X			
Hematology	D	7.2.2.5.	X	X			X	X		X	X			X	X[2]	X			

Visit name	Category	Protocol Section	Screening/ Baseline Period	Treatment Period												Follow-up Period[10]		
			Screening/ Baseline	Cycle 1				Cycle 2			Cycle 3				Subsequent cycles	EoT1	150 - Day Safety[6]	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**8**	**15**	**1**				
Chemistry	D	7.2.2.5.	X	X			X	X		X	X			X	X[2]	X			
Coagulation	D	7.2.2.5.	X	X				X			X				X[2]	X			
Thyroid function	D	7.2.2.5.	X	X				X			X				X[2]	X			
Plasma EBV DNA level	D	7.2.2.5.	X	X				X			X				X[2]	X			
Serology exam[8]	D	7.2.2.5.	X	X				X			X				X[2]	X			
Pregnancy test (serum or urine)	D	7.2.2.5.	X[3]					X			X				X	X			
	S																X[4]		
Cytokines (IFN-γ, IL-6, IL-1, TNF-α) for safety[9]	D	7.2.2.5.	X	When a suspected cytokine release syndrome, immediately after the AE, and one week after occurrence of the AE															
12-lead ECG[8]	D	7.2.2.6.	X	X							X								
Tumor evaluation as per **RECIST/irRC**	D	7.2.1.	X								**During treatment**: 8 weeks after Cycle 1 Day 1, and then every 8 weeks until week 40. Then every 12 weeks until progression or patient withdrawal. **Follow-up for progression**: Every 8 weeks until week 40, then every 12 weeks until progression or lost to follow-up.								
Newly obtained tumor sample during treatment	D	7.2.4.									Any time between C3D1 and End of treatment								
Blood sample for immunomonitoring	D	7.2.4.		X		X	X	X	X	X						X			
Blood sample for cytokine analysis	D	7.2.4.		X		X	X	X	X	X						X			
PDR001 infusion	D	6.1.		i.v. every 4 weeks															
PK sampling	D	7.2.3.		X	X	X	X	X	X	X	X	X	X	X	X[5]	X	X[7]		

Visit name	Category	Protocol Section	Screening/ Baseline Period	Treatment Period												Follow-up Period[10]		
			Screening/ Baseline	Cycle 1				Cycle 2			Cycle 3				Subsequent cycles	EoT1	150 - Day Safety[6]	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**	**2**	**8**	**15**	**1**				
IG sampling	D	7.2.3.		X				X			X				X[5]	X	X[7]		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5. 7.1.6. 7.1.7.															X	X	X
AEs/irAEs	D	8.	Continuous																
Survival contact (every 3 months)	D	7.1.7.																	X

[1]IVRS/IRT must be contacted to randomize the patient before receiving first dose on Cycle 1 Day 1 (within 72 hours of first dose).

[2]Every 12 weeks (cycles 3, 6, 9, 12, etc).

[3]To be performed within 72 hours before first dose.

[4] To be performed monthly

[5] Cycles 4, 5 and 6 only.

[6] Safety evaluations for 150 days after last dose of PDR001 with contacts at 30-, 90-, and 150-day. After initiation of new antineoplastic therapy, only AEs/SAEs suspected to be related to PDR001 will be collected. 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.

[7]only for patients who come to site for 150-day safety follow up visit.

[8] To be terminated upon implementation of Protocol Amendment 05.

[9] To be terminated upon implementation of Protocol Amendment 06.

[10] Assessments within follow-up period are not applicable to patients who transfer to another clinical study or an alternative treatment option to continue provision of study treatment.

Table 7-2 Visit evaluation schedule (patients in chemotherapy arm)

Visit name	Category	Protocol Section	Screening/. Baseline Period	Treatment Period					Follow-up Period		
			Screening/. Baseline	Cycle 1	Cycle 2	Cycle 3	Subsequent cycles	EoT1	30-Day Safety	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**1**	**1**	**1**				
Obtain Informed Consent	D	7.1.1.	X								
IVRS/IRT Registration	D	6.4.	X[1]								
Demography	D	7.1.1.2.	X								
Inclusion/ exclusion criteria	D	5.2/5.3.	X								
Newly obtained or archival tumor sample	D	7.2.4.	X								
Medical History	D	7.1.1.2.	X								
Diagnosis and extent of cancer	D	7.1.1.2.	X								
Prior antineoplastic therapy	D	6.3.1.	X								
Prior/concomitant medications	D	6.3.1.	X	Continuous							
Physical exam	S	7.2.2.1.	X	X	X	X	X[2]	X			
Vital signs	D	7.2.2.2.	X	X	X	X	X[2]	X			
Height	D	7.2.2.3.	X								
Weight	D	7.2.2.3.	X	X	X	X	X[2]	X			
ECOG Performance status	D	7.2.2.4.	X	X		X	X[2]	X			
Hematology	D	7.2.2.5.	X	X	X	X	X[2]	X			
Chemistry	D	7.2.2.5.	X	X	X	X	X[2]	X			
Coagulation	D	7.2.2.5.	X	X	X	X	X[2]	X			
Thyroid function	D	7.2.2.5.	X	X	X	X	X[2]	X			
Plasma EBV DNA level	D	7.2.2.5.	X	X	X	X	X[2]	X			
Serology exam[5]	D	7.2.2.5.	X	X	X	X	X[2]	X			
Cytokines (IFN-γ, IL-6, IL-1, TNF-α) for safety	D	7.2.2.5.	X								

Visit name	Category	Protocol Section	Screening/. Baseline Period	Treatment Period					Follow-up Period		
			Screening/. Baseline	Cycle 1	Cycle 2	Cycle 3	Subsequent cycles	EoT1	30-Day Safety	Disease progression	Survival
Day of cycle			**-28 to -1**	**1**	**1**	**1**	**1**				
Pregnancy test (serum or urine)	D	7.2.2.5.	X[3]		X[4]	X[4]	X[4]	X			
	S								X[4]		
12-lead ECG	D	7.2.2.6.	X								
Chemotherapy	D	6.1.		as prescribed regimen[4]							
Tumor evaluation as per RECIST v1.1	D	7.2.1.	X	**During treatment**: 8 weeks after Cycle 1 Day 1, and then every 8 weeks until week 40. Then every 12 weeks until progression or patient withdrawal. **Follow-up for progression**: Every 8 weeks until week 40, then every 12 weeks until progression or lost to follow-up.							
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5. 7.1.6. 7.1.7.							X	X	X
AEs	D	8.	Continuous								
Survival contact (every 3 months)	D	7.1.7.									X

[1]IVRS/IRT must be contacted to randomize the patient before receiving first dose on Cycle 1 Day 1 (within 72 hours of first dose).

[2]Every 12 weeks (cycles 3, 6, 9, 12, etc). More frequent evaluations may be performed at the investigator's discretion if medically indicated or if recommended by drug product information.

[3]To be performed within 72 hours before first dose.

[4] Investigators must refer to the approved label of the product.

[5] To be terminated upon implementation of Protocol Amendment 05.

Table 7-3 Visit evaluation schedule (crossover patients treated with PDR001)

Visit name	Category	Protocol Section	Treatment Period								Follow-up Period[8]		
			Cycle 1		Cycle 2		Cycle 3		Subsequent cycles	EoT2	150 - Day Safety[5]	Disease progression	Survival
Day of cycle			**1**	**15**	**1**	**15**	**1**	**15**	**1**				
IVRS/IRT Registration	S	6.4.	X[1]										
Prior/concomitantmedications	D	6.3.1.	Continuous										
Physical exam	S	7.2.2.1.	X	X	X	X	X	X	X[3]	X			
Vital signs	D	7.2.2.2.	X	X	X	X	X	X	X[3]	X			
Weight	D	7.2.2.3.	X		X		X		X[3]	X			
ECOG Performance status	D	7.2.2.4.	X				X		X[3]	X			
Hematology	D	7.2.2.5.	X	X	X	X	X	X	X[3]	X			
Chemistry	D	7.2.2.5.	X	X	X	X	X	X	X[3]	X			
Coagulation	D	7.2.2.5.	X		X		X		X[3]	X			
Thyroid function	D	7.2.2.5.	X		X		X		X[3]	X			
Plasma EBV DNA level	D	7.2.2.5.	X		X		X		X[3]	X			
Serology exam[6]	D	7.2.2.5.	X		X		X		X[3]	X			
Pregnancy test (serum or urine)	D	7.2.2.5.	X[2]		X		X		X	X			
	S										X[4]		
Cytokines (IFN-γ, IL-6, IL-1, TNF-α) for safety[7]	D	7.2.2.5.	When a suspected cytokine release syndrome, immediately after the AE, and one week after occurrence of the AE										
12-lead ECG[6]	D	7.2.2.6.	X				X						
Tumor evaluation as per **RECIST/irRC**	D	7.2.1.					**During treatment**: 8 weeks after Cycle 1 Day 1, and then every 8 weeks until week 40. Then every 12 weeks until progression or patient withdrawal. **Follow-up for progression**: Every 8 weeks until week 40, then every 12 weeks until progression or lost to follow-up.						
PDR001 infusion	D	6.1.	i.v. every 4 weeks										

Visit name	Category	Protocol Section	Treatment Period								Follow-up Period[8]		
			Cycle 1		Cycle 2		Cycle 3		Subsequent cycles	EoT2	150 - Day Safety[5]	Disease progression	Survival
Day of cycle			**1**	**15**	**1**	**15**	**1**	**15**	**1**				
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5. 7.1.6. 7.1.7.									X	X	X
AEs/irAEs	D	8.	Continuous										
Survival contact (every 3 months)	D	7.1.7.											X

[1]IVRS/IRT must be contacted to receive medication number for the first package of PDR001 treatment before first dose on Cycle 1 Day 1 (within 72 hours of first dose).

[2]To be performed within 72 hours before first dose.

[3]Every 12 weeks (cycles 3, 6, 9, 12, etc).

[4]To be performed monthly

[5] Safety evaluations for 150 days after last dose of PDR001 with contacts at 30-, 90-, and 150-day. After initiation of new antineoplastic therapy, only AEs/SAEs suspected to be related to PDR001 will be collected. 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.

[6] To be terminated upon implementation of Protocol Amendment 05.

[7] To be terminated upon implementation of Protocol Amendment 06.

[8] Assessments within follow-up period are not applicable to patients who transfer to another clinical study or an alternative treatment option to continue provision of study treatment.

7.1.1 Screening/baseline period

The study IRC/IEC informed consent form must be signed and dated before any screening/baseline procedures are performed, except for evaluations performed as part of standard of care.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 7-1, Table 7-2 and Table 7-3. Screening/Baseline assessments must be repeated if performed outside of the specified screening window (Section 7.1). The screening failure reason will be entered on the Screening Phase Disposition eCRF.

Submission of a newly obtained tumor sample (formalin fixed, in ethanol) or an archival tumor sample (should a newly obtained tumor sample not be possible for medical reasons) are requested and will be collected, whenever possible, from all patients at screening/baseline. For details refer to Section 7.2.4.

7.1.1.1 Information to be collected on screening failures

A patient who signed an Informed Consent Form 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.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during screening/baseline (see Section 8 for SAE reporting details) or died (Death eCRF should be completed) or withdrew consent (Withdrawal of consent eCRF should be completed).

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, Epstein–Barr virus (EBV) status and any other assessments that are done for the purpose of determining eligibility for inclusion in the study.

7.1.2 Treatment period

Patients will be randomized according to a 2:1 ratio, to either the investigational arm or the control arm. An effort should be made to ensure patients start treatment at the latest within 72 hours of randomization.

- **Investigational arm**: PDR001 at the RP2D as established in the [CPDR001X2101] phase I (first-in-human) study (400mg i.v.Q4W).
- **Control arm**: Commonly used chemotherapy as per investigator's choice.

For the purpose of scheduling and evaluations, a treatment cycle will consist of 28 days for patients treated with PDR001. Patients treated with PDR001 who meet the following criteria may continue treatment in additional cycles:

- Patients with a CR, PR or SD will continue to receive PDR001 until confirmed CR or until the patient experiences unacceptable toxicity.
- Patients with PD according to the RECIST v1.1 that has been confirmed but is not worsening and in stable or improved clinical status. These patients should remain under treatment until there is a further progression or clinical deterioration.

Note: Patients treated with PDR001 will **not** be discontinued from the study treatment due to progressive disease as per RECIST v1.1.

Accumulating evidence indicates that objective responses to immunotherapy follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while other target lesions are regressing ("mixed response") (Wolchock et al 2009). It is therefore reasonable to allow for these possibilities and continue to treat the patient until progression is confirmed and found to be advancing at the next imaging assessment as per immune-related Response Criteria (irRC). An outline of the irRC is provided in Appendix 2.

Example criteria for continuing treatment beyond progression are below:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

These considerations should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment. Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the patient is not benefiting from study treatment and cannot be managed by the addition of supportive care.

The decision to continue or stop treatment should be discussed with the Novartis Medical Responsible and will be documented in the study files.

Please refer to Table 7-1, Table 7-2 and Table 7-3 for details of the timing of required assessments and Section 7.1 for visit windows.

7.1.2.1 Crossover

Patients in the control arm will be allowed to crossover to PDR001 treatment if they have radiological progression (as per RECIST v1.1) documented by an independent central review and the investigator believes this is the best treatment option for the patient. The End of Treatment (EoT1) visit assessments should be performed as described in Section 7.1.3 before a patient can receive PDR001 treatment.

Patients should receive PDR001 within 21 days of the last radiological assessment, if they have no Grade 3/4 AEs and brain metastases. Each case must be first discussed with Novartis. No other antineoplastic therapies are allowed from the time of disease progression to the time of

crossover treatment initiation and throughout PDR001 treatment. Once transitioned to PDR001 treatment, patients will attend the clinic for treatment and safety monitoring as described in Section 7.2.2.

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 should make a reasonable 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. They may be considered discontinued if they state an intention to withdraw or fail to return for visits.

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 as per irRC (not as per RECIST v1.1; patients treated with PDR001)
- Progressive disease as per RECIST v1.1 (patients treated with chemotherapy)
- Confirmed Complete response as per RECIST v1.1(patients treated with PDR001)
- Study terminated by Novartis
- Patient/guardian decision
- Protocol deviation
- Technical problems

Study treatment must be discontinued 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 Treatment (EoT1) visit and then be discontinued from the study treatment (please refer to Table 7-1 and Table 7-3 for list of assessments to be performed).

Patients in the control arm, who switch to PDR001 treatment, should have an EoT visit (EoT2) once they are discontinued from PDR001 treatment (please refer to Table 7-3 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 should be completed, giving the reason for stopping the study treatment. End of treatment/Premature withdrawal visit is not considered as the end of the study. The investigator must also contact IRT to register the patient's discontinuation from study treatment.

Patients who discontinue study treatment should not be considered discontinued 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 7.1.8. 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.

Patients who transfer into another study or an alternative treatment option to continue provision of study treatment will perform the EoT procedures, but not any further study assessments.

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 any longer, and does not allow further collection of personal data.

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone calls, e-mail, letter) to determine the primary reason for this decision and record this information.

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

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

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

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

7.1.5 Follow up for safety evaluations

All patients in the PDR001 treatment arm must have safety evaluations for 150 days after the last dose of study treatment. Patient in the Chemotherapy arm must have safety evaluations for 30 days after the last dose of study treatment.

Patients in the control arm who crossover are not required to have a 30-day safety follow-up performed and can crossover as soon as the End of Treatment (EoT1) visit is complete. Once patients discontinue PDR001 crossover treatment, safety follow-up must be performed for 150 days after the last dose of PDR001.

The evaluations can be done either by telephone call or visit for the 30-, 90-, and 150-day safety follow-up visits for the PDR001 arm and crossover patients. 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. A PK and immunogenicity sample should be collected at 150 days for PDR001 arm patients only, as described in Section 7.2.3. If the 150-day safety evaluation is conducted by phone, samples do not need to be collected.

Data collected during the Safety follow up period should be added to the Adverse Events eCRF, Concomitant Medications eCRF, Antineoplastic therapies since discontinuation of study drug eCRF (including tumor directed surgical procedures) and Unscheduled blood collection for PK and IG eCRFs. All AEs suspected to be related to study treatment should be followed weekly, or as clinically indicated, until resolution or stabilization. For female patients of child bearing potential, pregnancy tests will be performed as outlined in Section 7.2.2.5.

The safety follow-up will not be performed for patients who transfer to another study or to an alternative treatment option to continue provision of study treatment.

7.1.6 Follow up for disease progression

All patients who discontinue study treatment for any reason other than:

- disease progression per irRC (for patients treated with PDR001)
- disease progression per RECIST v1.1 (for patients treated with chemotherapy)
- clinical deterioration, death, lost to follow up or consent withdrawal

should return for tumor evaluation assessments (please refer to Table 7-4) until disease progression, death, discontinuation from the study for any other reason (e.g., loss to follow-up or withdrawal of consent), the initiation of a new antineoplastic treatment, or until the End of the Study whichever occurs first.

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, e-mail or letter, to determine if the patient had disease progression. Once the Follow up for Disease progression period ended, the End of Post treatment Phase disposition eCRF should be completed.

Antineoplastic therapies or tumor directed surgical procedures initiated during the disease progression follow-up period must be recorded on the Antineoplastic therapies since discontinuation of study drug eCRF.

The disease progression follow-up will not be performed for patients who transfer to another study or to an alternative treatment option to continue provision of study treatment.

7.1.7 Follow up for survival

All patients will be followed for survival via a phone call, email or letter, every 12 weeks and up to one additional time per quarter if safety or regulatory needs, until any of the following (whichever occurs first): death, withdrawal of consent, loss to follow-up or at least 24 months from the first dose of study treatment. Antineoplastic therapies or tumor directed surgical procedures initiated during the survival follow-up period must be recorded on the Antineoplastic therapies since discontinuation of study drug eCRF.

The survival follow-up will not be performed for patients who transfer to another study or to an alternative treatment option to continue provision of study treatment.

7.1.8 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.

7.2 Assessment types

7.2.1 Efficacy assessments

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

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

Imaging data will be centrally collected in blinded fashion and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The results of the central evaluations will be used for primary analysis purposes. The local investigator's assessment will be used for treatment decision making (study discontinuation due to PD as per irRC for patients treated with PDR001). Patients in PDR001 treatment will not be discontinued from the study treatment due to progressive disease as per RECIST v1.1. Similar to RECIST v1.1, irCR and irPR must be confirmed at a new assessment after at least 4 weeks. In addition, unlike RECIST v1.1, irPD also requires confirmation at a new assessment after at least 4 weeks. Please refer to Appendix 1 and Appendix 2 for further details.

Patients in the control arm who progressed after chemotherapy are allowed to crossover to the PDR001 after their documented progression is confirmed as per RECIST v1.1 based on the independent central review.

The independent central review of imaging data will be terminated for the whole study when both criteria are met, 1) decisions are made based on central review results for all chemotherapy arm patients on whether to crossover; 2) all patients have reached a minimum of 12 months follow up after the first dose of study treatment (unless have been lost to follow-up).

The imaging assessment collection plan is presented in Table 7-4. Details of the central review process will be described in the independent review charter.

Table 7-4 Disease assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI with contrast enhancement (Chest, Abdomen, Pelvis)	Mandated	**During treatment**: 8 weeks after Cycle 1 Day 1, and then every 8 weeks until week 40. Then every 12 weeks until progression or patient withdrawal. **Follow-up for progression**: Every 8 weeks until week 40, then every 12 weeks until progression or lost to follow-up.
Brain CT or MRI with contrast	Mandated	If disease was detected at baseline, or if clinically indicated.

Screening/baseline assessments

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1).

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the screening/baseline images for this study. Any imaging assessments obtained after randomization cannot be considered screening/baseline images. At screening, all patients will undergo CT scan with i.v. contrast of the brain, chest, abdomen and pelvis. If there is clinical evidence of disease in the head and neck, a CT scan with i.v. contrast of the head and neck will also be performed. The assessments required at screening/baseline are indicated in Table 7-4.

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 scan 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/baseline, brain MRI or CT should be completed at the following assessments. 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/post-baseline imaging assessments

Imaging assessments as described in Table 7-4 should be performed using the same imaging modality used at screening/baseline, irrespective of study treatment interruption or actual dosing.

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/baseline 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 IV contrast media. At the discretion of the

Investigators, FDG-PET scans may be performed to document progressive disease per RECIST v1.1 (Appendix 1).

All study imaging (including any off-schedule imaging studies) should be submitted to the designated imaging CRO for analysis.

Timepoints at which progression is determined locally

All patients who have disease progression, determined by the local investigator require an expedited central review. Rapid image transmission to the imaging CRO may be accomplished by transferring the images electronically (e.g., via the Internet). In all instances, the process at the imaging CRO will ensure that the central reviewers remain blinded to the results of the local assessment and the expedited nature of the review. The investigator seeking an expedited review must indicate this request to the imaging CRO on a designated form or by alternative means. The imaging will undergo expedited central review (within 5 business days from the time of image receipt at the imaging CRO) and the results of the central review will be communicated to the site. While the investigator is awaiting the results of the central review, it is preferable that the patient continue on study treatment. However, during this time, the investigator should do whatever is medically necessary for the patient.

Note: If an investigator would like to discuss the central review results, there will be an independent physician at the imaging CRO, who is not part of the central review pool for this study. This independent physician will be able to discuss the central review findings with the investigator. The central reviewers are completely excluded from such discussion. The contact at the imaging CRO can arrange such a discussion, as specified in the manual provided by the designated imaging CRO.

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, thyroid function, pregnancy, ECG, as well as collecting of the AEs at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

Physical examination will be performed according to Table 7-1, Table 7-2 and Table 7-3.

At Screening/Baseline and Cycle 1 Day 1, prior to PDR001 infusion or chemotherapy, 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.

After Cycle 1 Day 1 and 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 informed consent must be included in the Medical History eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event eCRF.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before dosing (when the dose is taken/administered at the clinic) and as indicated in Table 7-1, Table 7-2 and Table 7-3 as per institutional standards. Vital signs should be assessed in the same position through the study.

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

7.2.2.3 Height and weight

Height and body weight will be measured as indicated in Table 7-1, Table 7-2 and Table 7-3 as per institutional standards.

7.2.2.4 Performance status

ECOG performance status will be assessed according to Table 7-5 and as indicated in Table 7-1, Table 7-2 and Table 7-3.

Table 7-5 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
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 (except Cytokines, Serology and EBV test examinations that will be evaluated centrally). Refer to Table 7-6 for a summary of the parameters to be evaluated.

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 for that laboratory.

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, 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 for the safety follow-up visits, a urine or serum pregnancy test will be performed at home or at a local doctor's office monthly and the results will be communicated to the site staff. The result will be recorded only in the source documentation, not in the CRF. A positive pregnancy test requires immediate discontinuation of study treatment. In addition, refer Section 8.3 for follow-up and reporting Pregnancies.

Table 7-6 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 (fasting) Magnesium, Inorganic Phosphate, Total Bilirubin (also measure direct and indirect bilirubin if total bilirubin is > grade 1), Blood Urea Nitrogen (BUN) or Urea
Coagulation	Prothrombin time (PT) or International Normalized Ratio (INR), Activated partial thromboplastin time (APTT)
Thyroid	Free T4, TSH (Thyroid Stimulation Hormone)
Cytokines[1, 2, 4]	Interferon-gamma (IFN-γ), Interleukin-6 (IL-6), Interleukin-1 (IL-1), Tumor necrosis factor-alpha (TNF-α)
EBV[2]	DNA levels in plasma
Serology exam in serum[2, 3]	Anti-DNA antibodies (Abs), Anti-nuclear abs, Anti-phospholipid abs, Anti-mitochondrial abs, c-Reactive protein (CRP), Rheumatoid factor (RF)
Pregnancy	Serum and/or urine samples only for women of childbearing potential
[1]To be performed at Screening/Baseline for all patients, and ad hoc (by ELISA), if cytokine release syndrome is suspected only for patients in PDR001 arm. [2] To be performed by a Central laboratory. [3] To be terminated upon implementation of Protocol Amendment 05. [4] To be terminated upon implementation of Protocol Amendment 06.	

7.2.2.6 Cardiac assessments (patients in PDR001 arm)

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as per the assessment schedule in Table 7-1, Table 7-2, Table 7-3 and Table 7-7. Blood samples scheduled at the same time point should be taken after the ECGs are completed. The ECGs on Day 1 of Cycles 1 and 3 must be performed in triplicate.

Table 7-7 12 lead ECG collection plan for central review (patients in PDR001 arm)***

Cycle	Day	Time
Screening/Baseline§	-28 to -1	Anytime (all patients)
1	1	*1h (±5 min) post-dose
3	1	*Pre-dose
3	1	*1h (±5 min) post-dose
Unscheduled**	-	Anytime

§ ECG at baseline should be performed for all patients.
* ECGs performed in triplicate.
** A PK sample should be collected just after an ECG performed due to an unexpected cardiac signal.
** Unscheduled ECGs could be performed for safety reasons for all patients.
*** This plan is only applicable to central ECG review, which is obsolete upon implementation of Protocol Amendment 05.

All ECGs will be independently reviewed by a central laboratory. Instructions for the collection and transmission of ECGs to the central ECG laboratory will be provided in the ECG Manual.

Upon implementation of Protocol Amendment 05, the ECG collection plan for central review as detailed in Table 7-1, 7-2, 7-3 and 7-7 is obsolete. Instead, ECGs are performed and reviewed locally, with the timing and frequency based on Investigator's judgement.

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

7.2.3 Pharmacokinetics and immunogenicity assessments (patients in PDR001 arm)

The following PK parameters may be determined for PDR001 using non-compartmental methods: Cmax, Tmax, AUC0-tlast (Cycle 1 and Cycle 3), time to last measurable concentration (Tlast), t1/2, and the accumulation ratio of PDR001.

PK data will be collected from all patients in the PDR001 arm using a sparse sampling scheme as described in Table 7-8. Details on IG sample collections are also included in this table.

If the dosing of Cycle 3 Day 1 is delayed, the PK sampling for the PK profile should be delayed accordingly to match the scheduled time points for Cycle 3 as outlined in Table 7-8. PK and IG 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) or if IG is suspected. No additional PK and IG samples (including EoT and unscheduled samples) will be collected from any patient once Cycle 4 PK and IG samples have been collected from all the PDR001 arm patients.

[redacted]

Note: PK or IG samples will not be collected for patients who crossover.

Table 7-8 Pharmacokinetic blood collection log (patients in PDR001 arm)

Cycle	Day	Scheduled Time Point (h)**	Analytes	PK Sample No	IG Sample No*
1	1	Pre-dose	mAb and IG	1	401
1	1	1h post-dose§ (± 5 min)	mAb	2	
1	2	24h post-dose§ (± 2h)	mAb	3	
1	8	168h post-dose§ (± 8h)	mAb	4	
1	15	336h post-dose§ (±24h)	mAb	5	
2	1	672h post-dose§ (±48h) /Pre-dose of cycle 2	mAb and IG	6	402
2	8	168h post-dose§ (± 8h)	mAb	7	
2	15	336h post-dose§ (±24h)	mAb	8	
3	1	672h post-dose§ (±48h) /Pre-dose of cycle 3	mAb and IG	9	403
3	1	1h post-dose§ (± 5 min)	mAb	10	
3	2	24h post-dose§ (± 2h)	mAb	11	
3	8	168h post-dose§ (± 8h)	mAb	12	
3	15	336h post-dose§ (± 24h)	mAb	13	
4	1	672h post-dose§ (±48h) / Pre-dose of cycle 4	mAb and IG	14	404
5	1	Pre-dose of cycle 5	mAb and IG	15	405
5	1	1h post-dose§ (± 5 min)	mAb	16	
6	1	Pre-dose of cycle 6	mAb and IG	17	406
6	1	1h post-dose§ (± 5 min)	mAb	18	
EoT			mAb and IG	5000	6000
Unscheduled (including 150-day safety follow-up visit)			mAb and IG	1001+	2001+

*IG samples are to be collected together with PK samples.
§After completion of the infusion.
**PK samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10mL of saline.

7.2.3.1 Bioanalytics

Bioanalysis for pharmacokinetic studies will employ 2 validated assays:

1. The assay to quantify PDR001 will be a validated LCMS. The details of the assay will be documented in the [CPDR001X2201 Laboratory Manual].
2. The assay to quantify and assess the IG will be a validated homogeneous ELISA. The details of the assay will be documented in the [CPDR001X2201 Laboratory Manual].

7.2.3.2 PK and immunogenicity sample handling, labeling, and shipping instructions

A total of 4 mL of blood will be collected at each time point. For time points when PDR001 (mAb) PK and IG are to be measured, a single blood sample will be collected for both IG and PDR001 PK. **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 [CPDR001X2201 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/Immunogenicity Blood Collection eCRF.

7.2.4 Biomarkers (patients in PDR001 arm)

In this study biomarker analyses will be used to investigate the effect of the PDR001 at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes. In addition, potential predictive markers of efficacy will also be explored.

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 tumor samples are outlined in the [CPDR001X2201 Laboratory Manual].

Note: on-treatment tumor or blood samples for biomarker analysis will not be collected for patients who crossover.

Table 7-9 Biomarker sample collection plan

Sample Type	Visit/ Time point	Slides/Volume	Marker*	Purpose
Tumor samples				
Newly obtained tumor sample or archival tumor block (if newly obtained tumor sample is not feasible) (**all patients**)	Screening/Baseline	Newly obtained formalin fixed tumor sample in ethanol (3-6 passes) or archival FFPE tumor block or a minimum of 15 freshly cut slides from archival paraffin tumor tissue	RNA expression of immune-related genes IHC expression of markers such as: PD-L1 LAG-3 TIM-3 CD8, Foxp3 TIL counts Protein expression of immune-related markers	Assess expression status of potential predictors of efficacy Pharmacodynamic markers (Baseline)
Newly obtained tumor sample (patients in PDR001 arm)	Any time between C3D1 and End of Treatment	Newly obtained formalin fixed tumor sample in ethanol (3-6 passes)	RNA expression of immune-related genes PD-L1, CD8, Foxp3 TIL counts Protein expression of immune-related markers	Pharmacodynamic effect (on-treatment)
Blood samples				
Blood sample for plasma cytokine analysis (patients in PDR001 arm)	C1D1 (pre-dose) C1D8 C1D15 C2D1 (pre-dose) C2D8 C2D15 End of Treatment	Approximately 5 mL	Cytokine analysis (e.g., IFN-γ, TNF-α, IL-6)	Pharmacodynamic effect (on-treatment)
[redacted]				

Note: On days and time points when biomarker and pharmacokinetic blood samples are being collected, the PK sample must be drawn first (patients in PDR001 arm).
*Markers are listed according to level of priority.

7.2.4.1 Tumor collection

7.2.4.1.1 Potential predictive markers

The status of immune checkpoint targets and cell populations will be analyzed in newly obtained or archival tumor sample. Expression and localization of biomarkers including but not limited to PD-L1 and CD8+ TIL counts may be measured by immunohistochemistry (IHC) or using additional techniques deemed suitable. Other related biomarkers may also be analyzed from this sample, depending on sample availability, resources, and patient's outcomes and as new scientific evidence becomes available.

Submission of an archival specimen or newly obtained tumor sample (formalin fixed, in ethanol) will be requested at screening/baseline (a fresh tumor sample is preferred), unless agreed differently between Novartis and the Investigator. A corresponding pathology report should be included along with the archival samples.

Archived tumor samples may be returned to the pathology laboratory at the end of the study, or at any time, at the request of the Investigator.

7.2.4.1.2 Pharmacodynamic markers (patients in PDR001 arm)

Pharmacodynamic assessments in tumor samples

For pharmacodynamic assessments, collection of evaluable newly obtained on-treatment tumor samples between Cycle 3 Day 1 and End of Treatment is recommended, and if site of disease is accessible. Exceptions may be made on a case by case basis after discussion between Novartis and the Investigator.

The pre- and on-treatment paired tumor samples will be used to assess PDR001 target modulation with established immunohistochemical methods and RNA expression analysis.

Additional markers or methods may be utilized if indicated by new findings from the literature as well as from Novartis internal data.

7.2.4.2 Blood sample collection (patients in PDR001 arm)

Blood samples will be collected as specified in Table 7-9 to characterize markers of activation in immune cells and circulating levels of cytokine in plasma.

All blood samples will be collected and processed as described in the [CPDR001X2201 Laboratory Manual].

[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 6.2.2.

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events 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 chemotherapy and 150 days following the last dose of PDR001 treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study (but is collected as a seriousness criterion); rather, information about deaths will be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient 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:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1. 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.

After initiation of new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected in the Adverse Events CRF.

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 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

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

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

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

SAE collection will start upon signing the informed consent whether the patient is a screen failure or not. 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 chemotherapy and 150 days after the patient has stopped PDR001 treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days in Chemotherapy arm or 150 days in PDR001 treatment 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. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

Information about all SAEs (either initial or follow-up information) is collected and recorded within the Electronic Data Capture (EDC) system. Data are required to be entered in English by designated investigator site staff in the eSAE Case Report Form (CRF). The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several drugs).

SAEs (initial and follow-up) that are recorded electronically in the EDC system should be entered and saved within 24 hours of awareness of the SAE. Data required for safety reporting will be transferred directly to the Novartis Chief Medical Office and Patient Safety (CMO&PS) Department. Follow-up information should be provided by updating the eSAE Case Report Form.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff.

CMO&PS staff review the data entered into the eSAE CRFs for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the queries and confirm or correct the data.

The Investigator must certify that the data entered into the electronic eSAE Report Forms are complete and accurate prior to database lock. After database lock, the investigator will receive copies of the eSAE data for archiving at the investigational site.

The paper SAE Form may also be used in case of technical emergencies in order to report an SAE within 24 hours. As soon as the technical issues are overcome, the SAE should also be

entered via the eSAE CRF. The paper SAE Form may also be used for all new and follow up cases at the request of Novartis.

If the SAE is not previously documented in the [PDR001 Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis 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.

When pregnancy occurs in a patient in the study, as general rule the study drug must be discontinued, though the patient may stay in the study and follow the assessments, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments. In exceptional cases, such as a women responding to the lifesaving treatment, the study drug can be continued.

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.

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.

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

An Independent Data Monitoring Committee (IDMC) will not be formed for this open-label phase II 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 based on the available data in the clinical database.

The data will be discussed with investigators in teleconferences, if deemed needed by the Novartis team. In case of having sufficient evidence of lack of efficacy for the study drug, Novartis and the investigator parties must reach a consensus on whether to terminate further patient enrolment in the treatment group.

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 (PPOS)) 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 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 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 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.

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/baseline 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 primary analysis of PFS will be performed for the comparison of PDR001 with the control arm. The cutoff date for the primary analysis is after approximately 70 PFS events have occurred across both of the two arms combined (approximately 114 patients randomized). This analysis will include the primary and selected secondary endpoints of the study, as defined in the RAP.

The following rules will be followed for reporting results unless stated otherwise: data will be summarized and listed by study arm. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

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 collected, Section 7.1.1, will not be included in any analysis, but will be reported in the CSR as separate listings.

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each patient. Other missing data will simply be noted as missing on appropriate tables/listings.

Data analysis after crossover

For patients who crossover to PDR001 after progression as per RECIST v1.1 to chemotherapy in the control arm, the data will be presented in listings separately from the randomized part of the study. If there are at least 10 patients crossing over, summary tables may be presented with frequency count and percentage for categorical data and descriptive statistics for continuous data. For these patients, the date of their first dose of PDR001 will be used as the starting date to define their safety and efficacy endpoints (such as ORR, irPFS and OS). Details will be provided in the RAP.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment (and strata) they have been assigned to during the randomization procedure. The FAS will be the primary population for all efficacy related data analyses.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication and have at least one valid post-screening/post-baseline safety assessment. Patients will be analyzed according to the study treatment (regimen) they actually received. The statement that a patient had no AEs (on the AE eCRF) constitutes a valid safety assessment. 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
- If the assigned treatment was never received, then the first treatment received when starting therapy with study treatment will be used for classification

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

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

10.1.3 Per-Protocol Set

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

- Treatment according to the randomization scheme (see Section 6).
- Presence of at least one measurable lesion at screening/baseline according to RECIST v1.1 as per Appendix 1.
- At least 2 post-screening/post-baseline tumor assessments (unless disease progression is observed before that time).

- Have not been previously treated with PD-1- or PD-L1-directed therapy or any therapeutic cancer vaccine.

Patients will be classified according to treatment received.

The PPS 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 below will not be performed.

All protocol deviations leading to exclusion from the PPS will be detailed in the RAP.

10.1.4 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have at least one dose of PDR001 and have at least one evaluable concentration measurement of PDR001. The PAS will be used for all PK analyses.

Note: Patients may be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of analysis along with their reason for removal.

10.2 Patient demographics/other screening/baseline characteristics

Demographic and other screening/baseline data including age, gender, height, weight, medical condition, and disease characteristics will be summarized descriptively by treatment arm on the FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

The actual dose and duration in days of PDR001 and as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized by means of descriptive statistics. Categories for relative dose intensity of 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 falling in each category will be presented. The summary data will be presented for each treatment cycle individually, as well as for all study days as a single category using descriptive statistics (e.g. mean, median, and modal doses). Similar analysis will be performed for the patients included in the control arm.

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.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized by treatment group/study arm. Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions, see Section 10.5.

10.4 Primary objective

The primary objective of the Phase II study is to assess any improvement in the anti-tumor effects of the PDR001 versus investigator's choice of treatment in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic NPC who progressed on or after first-line therapy.

10.4.1 Variable

The primary efficacy endpoint in this study is progression-free survival (PFS) based on central review of tumor scan, as defined per RECIST v1.1 (Appendix 1).

PFS is the time from the date of randomization to the date of event defined as the first documented confirmed 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.

10.4.2 Statistical hypothesis, model, and method of analysis

Patients are randomized in 2:1 ratio into either PDR001 arm or control arm. The primary efficacy endpoint, PFS as determined based on the central tumor assessment per RECIST v1.1, will be analyzed by study arm. Assuming proportional hazards for PFS, the following statistical hypothesis will be tested to address the primary efficacy objective:

$$H_{01}: \theta_1 \geq 1 \quad \text{vs.} \quad H_{A1}: \theta_1 < 1$$

where θ_1 is the PFS hazard ratio (PDR001 arm vs control arm). The analysis to test this hypothesis will consist of a stratified log-rank test at an overall one-sided 10% level of significance. The stratification factor is disease status (locally advanced recurrent NPC vs. metastatic NPC).

As a supportive analysis, a Bayesian Cox proportional hazard (PH) model (see Appendix 3) will be used to estimate the hazard ratio for PFS between the two treatment combination arms. The final analysis will be performed when 70 events (progressive disease or death due to any cause) are observed from the study.

An evidence-based prior for the non-parametric, interval-specific hazards of the control arm in the Bayesian Cox PH model is derived using available historical PFS data from the list of the phase II studies (see Table 1-1 and Appendix 3), using the meta-analytic-predictive (MAP) approach (Neuenschwander et al 2010) with the assumption of moderate/large between-trial heterogeneity. For more details about the model specification including the prior derivation and its operating characteristics please refer to Appendix 3.

Based on the historical studies, the median PFS for the patients in the control arm is assumed to be 5.5 months (165 days).

The dual-criterion for success based on Bayesian Cox PH model is defined to show a positive result if there is enough evidence that monotherapy PDR001 is superior to the control with respect to the primary PFS endpoint, such that:

- Posterior probability (HR > 1) < 10%, and
- Posterior median HR < 0.7

The posterior median of the HRs along with the associated 95% two-sided credible intervals will be produced for the treatment comparison of PDR001 to the control. In addition, the posterior probability that the true HR lies in the following intervals will be produced:

- Substantial efficacy: [0, 0.55)
- Moderate efficacy: [0.55, 0.7)
- Slight efficacy: [0.7, 1)
- No efficacy: [1, ∞)

Moreover, Kaplan-Meier plots will be provided in order to present PFS graphical outputs for the PDR001 and the control arm. KM estimates of the median and PFS rates at 2, 4, 6, 8, 10 and 12 months will be given along with 95% confidence intervals. The FAS will be used for the primary analysis. A stratified Cox regression model will also be used to estimate the HR of PFS as supplementary analysis,

10.4.3 Handling of missing values/censoring/discontinuations

If a patient has not had a PFS event at the time of analysis, he/she will be censored following the rules defined in RECIST v1.1 (please refer to Appendix 1).

10.4.4 Supportive analyses

The PPS will be used in a supportive analysis of the primary endpoint.

Additional [redacted] supportive analyses will be conducted if appropriate and defined in the RAP.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not Applicable.

10.5.2 Other secondary efficacy objectives

Efficacy endpoints ORR, BOR and TTP will be also assessed. irPFS will be derived using irRC (Appendix 2) based on central assessments. An immune related progression disease (irPD) is confirmed by 2 repeated scans at least 4 weeks apart from date of first documented irPD, and the date of 1st scan is defined as the date of irPD.

Individual lesion measurements, overall lesion response, duration of response (DOR), BOR, irPFS and OS will be listed by patient. BOR and ORR will be summarized by treatment arm with accompanying 95% confidence intervals. OS and DOR will be presented descriptively using Kaplan Meier plots. Median OS and DOR will be estimated along with 95% confidence

intervals. The OS rates along with 95% CIs will be provided at 6, 12, 18 and 24 months for each treatment arm using the Kaplan Meier distribution. A stratified Cox regression model will be used to estimate the HR of PDR001 arm vs. the control arm in OS and irPFS, respectively, along with 95% CI for HR.

10.5.3 Safety objectives

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.

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study treatment
3. post-treatment period: starting at day 31 after last dose 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 for PDR001 treatment and for a period of 30 days for chemotherapy. 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 (Section 10.5.3.2).

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/baseline) 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, and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group.

The following summaries will be produced for the combined on-treatment and post-treatment periods: AEs related to the study treatment by preferred term; SAEs related to the study treatment by preferred term; AEs of special interest related to the study treatment.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by CTCAE version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where Grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

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

ECG (patients in PDR001 arm)

- Shift table screening/baseline to worst on-treatment result for overall assessments.
- Listing of ECG evaluations for patients treated with PDR001 with at least one abnormality.

Vital signs

Definitions of notably abnormal results have to be part of the CDP, MAP, CSP and RAP.

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

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 study treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed by patient and summarized. Cumulative dose, dose intensity and relative dose intensity of PDR001 will be listed by patient and summarized.

10.5.4 Pharmacokinetics (patients in PDR001 arm)

The pharmacokinetic parameters that may be assessed are presented in Table 10-1. PK parameters will be determined for all PK-evaluable patients by non-compartmental method(s) using Phoenix (Pharsight, Mountain View, CA). PK parameters listed in Table 10-1 will be calculated and reported, when feasible for PDR001. Concentrations will be summarized by time and in each treatment arm.

Table 10-1 Noncompartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCinf	The AUC from time zero to infinity (mass x time x volume^{-1})
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the plasma (volume x time^{-1})
Vz	The apparent volume of distribution during terminal phase (associated with λz) (volume)

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

Pharmacokinetic variables:

The following pharmacokinetic parameters may be determined by profile using non-compartmental method(s) for PDR001:

- AUCinf, AUC0-last, Cmax, Tmax, T1/2, CL and Vz.

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the lower limit of quantitation (LLOQ) or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

Descriptive statistics of all pharmacokinetic parameters may include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges may be given for this parameter.

Summary statistics will be presented for PDR001 serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration versus time profiles and mean concentration versus time profiles will be generated.

Further analyses may be conducted using population PK approaches. In addition, a model based approach may be used to explore the potential relationship between efficacy, safety, and/or biomarker endpoints and PDR001 concentration and/or exposure metrics. Any analyses performed will be specified either in the RAP prior to clinical database lock or in a stand-alone analysis plan document. All analyses will be reported either in the CSR or a stand-alone report.

10.5.4.1 Data handling principles

Missing concentration values will be reported as is in data listings. Concentration values below 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.

10.5.5 Immunogenicity – exposure and/or adverse event relationship

Immunogenicity data may be analyzed for patients in PDR001 arm. Listing of immunogenicity evaluations will be provided.

The concentration/adverse event – immunogenicity relationship may be explored graphically, tabulated and if appropriate, evaluated by a mixed effects model in order to characterize a relationship between the changes from screening/baseline immunogenicity presence and serum concentration of PDR001.

In addition, the potential correlation between immunogenicity and other endpoints (major safety, efficacy and biomarker parameters) may be evaluated. This may be done in two steps. First, a descriptive analysis may be performed graphically between immunogenicity change from screening/baseline values and major safety, efficacy, and biomarker parameters (either as categories or continuous variables). [redacted]

10.5.6 Biomarkers in plasma and in tumor (patients in PDR001 arm)

PD markers in plasma

Pharmacodynamic markers, including soluble ligands and cytokine levels (e.g. IFN-γ, TNF-α, IL-6) will be assessed using plasma samples on-treatment (between C1D1 and C2D15) and at End of Treatment. Assessments will be listed by patient and summarized (when sample size is sufficient) using descriptive statistics. Any association/correlation analyses with other endpoints (PK, early clinical activity) will be detailed in the RAP.

PD markers in tumor

Pharmacodynamic markers, including CD8, Foxp3, TIL counts, RNA expression of immune-related genes, and protein expression of immune-related markers (e.g. IFN-γ) will be assessed using paired tumor samples at screening/baseline and on-treatment (between C3D1 and End of treatment). Assessments at screening/baseline and on-treatment and change from baseline will be listed by patient and summarized (when sample size is sufficient) using descriptive statistics.

Any association/correlation analyses with other endpoints (PK, early clinical activity) will be detailed in the RAP.

PD-L1 and potential predictors of efficacy in tumor

The expression levels of PD-L1, LAG-3 and TIM-3, at screening/baseline will be listed and summarized. The correlation between baseline PD-L1 expression and anti-tumor activity will be explored. Statistical analyses to assess the relationship between biomarker endpoints (PD-L1, LAG-3, TIM-3) and clinical endpoints (e.g. ORR, PFS) will be described in the RAP. All other biomarker data will be listed or summarized as appropriate.

10.7 Interim analysis

No formal interim analyses are planned.

10.8 Sample size calculation

Assuming a 2:1 randomization ratio of PDR001 vs. Comparator, 70 events (PD or death) are to be observed in the randomized Phase II to provide 85% power to detect a 0.55 hazard ratio in terms of PFS (corresponding to a median PFS of 10 months in PDR001 group and 5.5 months in the Comparator group), using a log-rank test at a 1-sided significance level of 0.1.

The final primary analysis of PFS will be done using a Bayesian proportional hazard model when there are at least 70 events observed. Based on the simulation results under different scenarios (see Appendix 3), 70 events provide reasonable operating characteristics in terms of the probability of obtaining a positive result (as defined in Section 10.4.2). Using the Bayesian

Cox PH model with mixture MAP prior for the yields reasonable 1-sided type I error (0.081) assuming no efficacy (HR=1) and power (0.92) assuming substantial efficacy (HR=0.55) when current data is in alignment with historical data.

Considering a uniform recruitment time of about 14 months and a 15% drop out rate at 12 months, approximately 114 patients need to be randomized in a 2:1 ratio to the two arms in order to observe 70 events after approximately 6 months follow up (approximately 20 months after FPFV):

- 76 patients to the PDR001 arm
- 38 patients to the control arm

EAST® trial design software v5.4 is used to compute the sample size.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

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

[redacted]

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 7.1.3 and Section 4.3.

11.5 Publication of study protocol and results

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

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

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

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

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

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of 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.

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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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List of Contributors

Authors (Version 3.1): [redacted]

Authors (Version 3): [redacted]

Authors (Version 2): [redacted]

Authors (Version 1): [redacted]

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
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
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.

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 intravenous (i.v.) contrast.

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

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

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when 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 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]

[1.] SOD for CR may not be zero when nodal lesions are part of target lesions

[2.] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR

[3.] Methodology change See Section 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.
- **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 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]
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.

- 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.

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.

- 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 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.

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)

[1]=Definitions can be found in Section 14.1.3.2.7.
[2]=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.3.2.7.
[3]=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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.

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
- 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 investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

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.

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

*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, 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, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer; Vol.45: 228-47.

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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.

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 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.

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.

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)

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.

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.

14.3 Appendix 3: Bayesian Cox proportional hazards model with meta-analytic-predictive prior and operating characteristics of the design

14.3.1 Introduction

In the following, the statistical model and prior distributions for the Bayesian Cox proportional hazard (PH) model will be described. We consider here the use of historical data of the same patient population (with moderately differentiated/undifferentiated, locally advanced recurrent or metastatic NPC) to enrich control arm.

14.3.1.1 Model specification

The primary analysis of progression free survival (PFS) will be based on a Bayesian Cox PH model. This model will be used to estimate the hazard ratio for PFS of PDR001 vs. SOC. This model assumes that the hazard function of individual in treatment group i (PDR001 or SOC) can be expressed as;

$$\lambda_i(\mathrm{t}) = \lambda_0(t)e^{\beta X_i}$$

Here λ_0 (t) is the baseline hazard (or hazard for SOC), X_i indicates the treatment group membership (0 for SOC and 1 for PDR001) and β denotes the log hazard ratio (HR) between PDR001 group and the SOC group. Furthermore baseline or SOC group hazard function λ_0 (t) is modeled via a piece-wise exponential model. This is a semi-parametric model which subdivides time into reasonably small K intervals and assumes that the baseline hazard is constant in each interval. i.e.,

for $$\lambda_0(t) = \lambda_{ck} \quad t \in (I_{k-1}, I_k] \qquad k = 1,2,\ldots..,K$$

Note that the λ_{Ck} refer to hazard for unit time (per day). Sampling model (or likelihood) under this framework can be constructed using Binomial distribution. In this model for each of the K time intervals, the number of events in the SOC group (r_{Ck}) and PDR001 group (r_{Tk}) follow Binomial distributions with interval-specific hazards λ_{Ck}. Under the proportional hazards assumption it follows that

SOC data:	$r_{Ck} \sim \text{Binomial}(n_{Ck}, 1 - e^{-\lambda_{Ck}L_k})$,
PDR001 data:	$r_{Tk} \sim \text{Binomial}(n_{Tk}, 1 - e^{-\lambda_{Ck}e^{\beta}L_k})$

where n_{Ck} and n_{Tk} are risk sets for event in the SOC and PDR001 groups, respectively, in interval $(I_{k-1}, I_k]$ and L_k is the length of the k-th interval.

The study plans to enroll approximately 114 patients to accrue 70 events for the primary analysis of PFS endpoint. This study will be considered successful if there is sufficient evidence that the monotherapy of PDR001 is superior to SOC in PFS based on the evaluation criteria, i.e.:

- Posterior probability (HR>1) < 10%, and
- Posterior mean HR<0.7.

14.3.1.2 Prior distribution

The Bayesian approach requires the specification of prior distributions for the model parameters. In this section we illustrated the specification of informative prior for interval specific hazards (λ_k's) using relevant data for SOC from publications and non-informative prior for log hazard ratio (β).

14.3.1.2.1 Prior for log hazard ratio (β)

The prior distribution for the log hazard ratio β was assumed non-informative, $\beta \sim N(\text{mean}=0, \text{sd}=10)$.

14.3.1.2.2 Prior derivation for interval specific hazard (λ_k 's)

A robust mixture prior will be used for interval specific hazards (λ_k's). An evidence-based prior for the interval-specific hazards of the controls in the Bayesian Cox PH model is derived using a robust meta-analytic-predictive (MAP) approach (Neuenschwander et al 2010; Schmidli et al 2014). The robust prior is a mixture prior with two components. The first component, derived from historical data, is a meta-analytic-predictive (MAP) prior (MAP component). The second component of the mixture prior (Weakly informative component) ensures further robustness against prior-data conflict to the control in the current trial.

- MAP component: Obtained from the published Kaplan Meier (KM) curves of 7 published studies using the meta-analytic predictive (MAP) approach.
- Weakly informative component: Reflecting the historical hazard rate for the controls but allowing for considerable prior uncertainty to handle possible prior-data conflict to the control arm in the current trial.

Further details are provided below.

MAP component

PFS data for SOC from 7 published studies were used to derive prior for interval specific hazards using MAP approach (Neuenschwander et al 2010). Table 14-7 provides the historical data from the 7 studies of SOC treated in a total of 212 patients. These 7 trials were chosen from the 11 historical studies listed in Table 1-1 of the study protocol for deriving the MAP prior. The other 6 trials were not used since the KM plots (estimates) were not available as required by the MAP approach.

Table 14-7 Historical PFS data from 7 studies

Chua et al (2003).

Time (days)	Prob. of remaining progression free	# patients at risk	# patients censored	# events
0	1	17		
30	0.76	13	0	4
60	0.70	12	0	1
90	0.64	11	0	1
120	0.59	10	0	1
150	0.47	8	0	2.
180	0.35	6	0	2
240	0.21	4	0	2
300	0.21	4	0	0
360	0.21	4	0	0

Foo et al (2002).

Time (days)	Prob. of remaining progression free	# patients at risk	# patients censored	# events
0	1	27		
30	0.96	26	0	1
60	0.88	24	0	2
90	0.85	23	0	1
120	0.77	21	0	2
150	0.53	14	0	7
180	0.39	10	0	4
240	0.28	8	0	2
300	0.12	3	1	4
360	0.12	3	0	0

Ngeow et al (2011).

Time (days)	Prob. of remaining progression free	# patients at risk	# patients censored	# events
0	1	30		
30	0.96	29	0	1
60	0.67	20	0	9
90	0.64	19	0	1
120	0.53	16	0	3
150	0.50	15	0	1
180	0.40	12	0	3
240	0.11	3	0	9
300	0.07	2	0	1
360	0	0	0	2

Peng et al (2013).

Time (days)	Prob. of remaining progression free	# patients at risk	# patients censored	# events
0	1	48		
30	1	48	0	0
60	1	48	0	0
90	0.98	47	0	1
120	0.88	42	0	5
150	0.77	37	0	5
180	0.38	18	0	19
240	0.03	1	0	17
300	0.03	1	0	0
360	0.03	1	0	0

Poon et al (2005).

Time (days)	Prob. of remaining progression free	# patients at risk	# patients censored	# events
0	1	28		
30	1	28	0	0
60	0.58	16	0	12
90	0.53	15	0	1
120	0.40	11	0	4
150	0.26	7	0	4
180	0.11	3	0	4
240	0.11	3	0	0
300	0.05	2	0	1
360	0.003	0	1	1

Wang et al (2006).

Time (days)	Prob. of remaining progression free	# patients at risk	# patients censored	# events
0	1	39		
30	0.95	37	0	2
60	0.85	33	0	4
90	0.80	31	0	2
120	0.69	27	0	4
150	0.56	22	0	5
180	0.46	18	0	4
240	0.38	15	0	3
300	0.28	11	0	4
360	0.18	7	0	4

Zhang et al (2008).

Time (days)	Prob. of remaining progression free	# patients at risk	# patients censored	# events
0	1	32		
30	0.99	32	0	0
60	0.79	25	1	6
90	0.66	21	0	4
120	0.52	17	0	4
150	0.52	17	0	0
180	0.37	12	0	5
240	0.15	5	0	7
300	0.07	2	0	3
360	0.01	0	0	2

In each of the 9 time intervals of the 7 historical trials, the number of events in the SOC group follows a Binomial distribution with interval-specific SOC hazards λ_{hCk} h=1,2,…7 (as stated in previous section):

Historical SOC data: $r_{hCk} \sim \text{Binomial}(n_{hCk}, 1 - e^{-\lambda_{hCk} L_k})$,

The meta-analytic-predictive prior for the log-hazards $\log(\lambda^*_{Ck})$ of the SOC arm in the current trial is obtained by analyzing the historical SOC data and using predictive distribution. The key assumption of this approach is similarity (not equality) of time-specific hazards in historical and current studies, λ_{hCk} and λ^*_{Ck}, h= 1,..7 and k=1,…9. The degree of similarity is formally expressed via exchangeability (Spiegelhalter 2004) i.e.

$\log(\lambda_{1Ck})$, ……, $\log(\lambda_{7Ck})$, $\log(\lambda^*_{Ck}) \sim \text{Normal}(\mu_k, \tau^2)$.

with population mean μ_k and between-trial standard deviation τ for the log-hazards for the k-th time interval in the SOC group. After considering the clinical context such that unrealistically large values of τ (eg., > 1) have small probability (eg., 5%), it was decided to assume the degree of similarity as

$$\tau \sim \text{log-normal}(\text{mean}=\log(0.5), \text{sd}=0.354)$$

This prior distribution has median 0.5, which amounts to moderate to large heterogeneity, and 95% probability interval (0.25,1.00), which covers a range of moderate to large heterogeneity (Spiegelhalter et al 2003).

Moreover in order to explore the related structure we modeled each μ_k by relating to neighboring by a μ_{k-1} linear model. The model assumes the following functional form

$$\mu_k \sim N(\eta_\kappa, \sigma^2_\kappa)$$

$$\eta_k = \eta_{k-1} + \rho_{k-1} \qquad k= 2, 3,……..9$$

Prior for η_1 is assumed to be N(mean=-1.386,sd=0.353) and $\rho_{k-1} \sim$ N(mean=0, sd=1), and $\sigma^2_\kappa = \omega * 0.353^2$ with $\omega \sim$ Uniform(0,1). This uses similar formulation as Krams et al (2005).

As mathematical closed form are not tractable statistical inference for the log-hazards of the SOC group in the new trial, $\log(\lambda^*_{Ck})$, was obtained using WinBUGS. Note that for PFS times

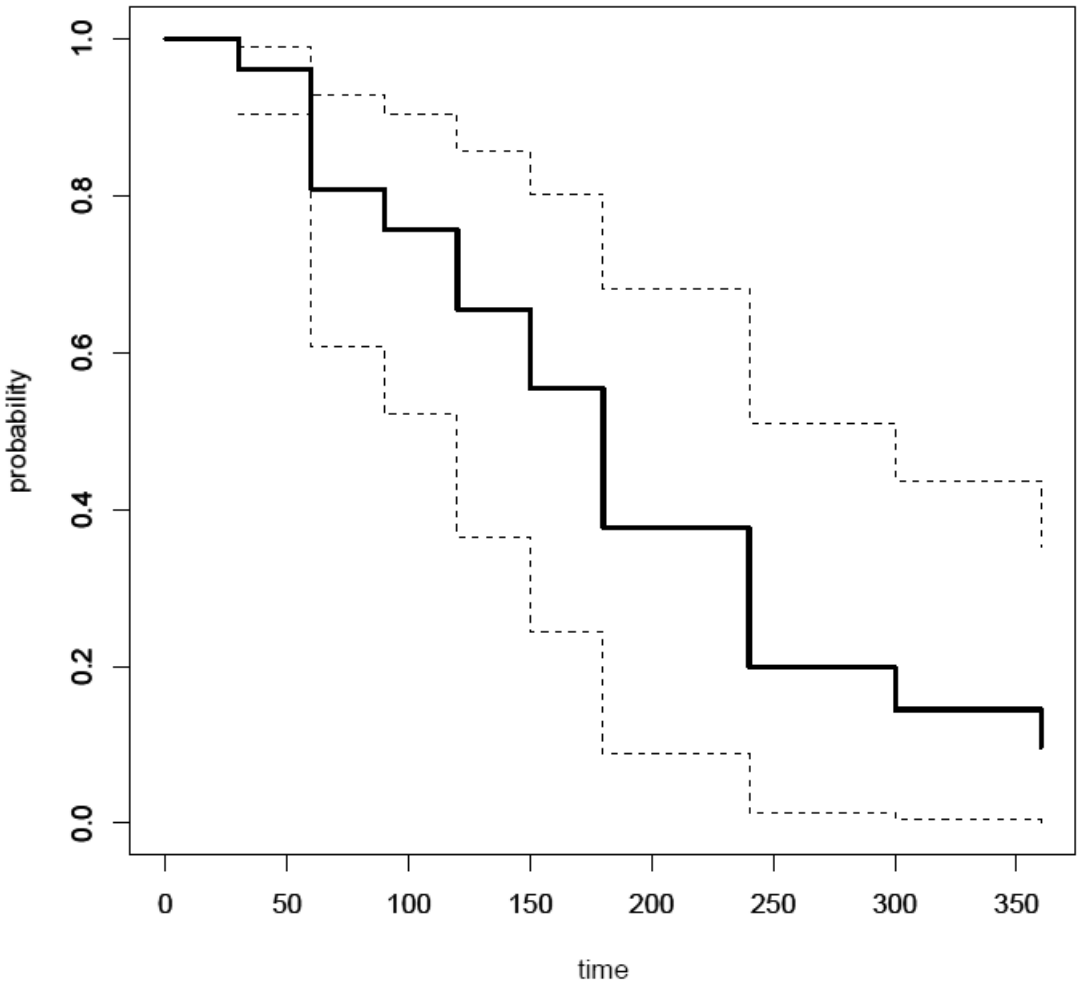
that exceed 360 days (the maximum time in the historical data set), the prior for these log-hazards is assumed equal mean to the prior from the last available log-hazard, i.e., λ^*_{C9} but greater standard deviation. Table 14-8 displays the prior summaries of the log-hazards (per day).

Table 14-8 Prior distribution of daily long-hazards

Time interval (days)	Log-hazards	
	Mean	**SD**
1-30	-6.771	0.560
31-60	-5.245	0.484
61-90	-6.202	0.538
91-120	-5.376	0.501
121-150	-5.206	0.494
151-180	-4.298	0.479
181-240	-4.399	0.480
241-300	-5.055	0.531
301-360	-4.752	0.571
360-420	-4.752	1.151
420-480	-4.752	2.080
480-540	-4.752	3.054

Figure 14-1 shows the prior progression free survival probabilities and 95% credible interval (dotted line). This shows that the prior median in around 5.5 months.

Figure 14-1 Prior distribution of corresponding progression free survival probabilities



Weakly informative component

When considering the use of historical controls in the current trial, a careful selection of the historical trials is necessary to render the exchangeability assumption for the SOC parameters plausible. Nevertheless, one has to acknowledge the possibility of prior-data conflict. Hence, we consider a robust version of the MAP prior by assuming a weakly informative prior for $\log(\lambda_{Ck})$ as N(mean=-6.771, sd=3). This allows to take into account the additional uncertainties.

Mixture prior

To obtain the mixture prior, 50% weight will be assigned to the MAP component, and 50% weight will be assigned to the weakly informative component to be more on conservative side to handle possible prior data conflict.

14.3.2 Operating characteristics

The purpose of this section is to present the operating characteristics of the proposed design under various scenarios. The data for the SOC arm are simulated such that for some scenarios they are in alignment with the historical control data and for the others, they are not. Ddifferent magnitudes of efficacy are also considered, e.g, no efficacy, moderate efficacy and substantial efficacy under different scenarios. Type I error rate and power for this design under different scenarios will be investigated as mentioned in details in the next section.

14.3.2.1 Scenarios investigated

In order to investigate the operating characteristics, data are simulated under the scenarios as described in Table 14-9.

Table 14-9 Different scenarios of operating characteristics simulations

Scenario#	Current control aligned with prior?	Efficacy Magnitude	Median PFS, SOC arm (months)	Median PFS, PDR001 arm (months)	True Hazard Ratio
1	Yes	No efficacy	5.5	5.5	1
2	Yes	Substantial	5.5	10.0	0.55
3	Yes	Moderate	5.5	8.2	0.67
4	No	No efficacy	7.5	7.5	1
5	No	Substantial	7.5	13.6	0.55
6	No	Moderate	7.5	12.9	0.67

As shown in the Table 14-9, SOC data are simulated to be aligned with the prior for scenarios 1-3. Ddifferent magnitudes of efficacy will be tested in these three scenarios by varying the true hazard ratio. For scenario 1, hazard ratio 1 means that there is no efficacy. The simulation output in this case provides Type I error rate. For the other two scenarios, powers are obtained. Similarly for scenarios 4-6, controlled data not aligned with prior are simulated and scenario 4 is the case with no efficacy where the simulation results provides Type I error rate.

14.3.2.2 Simulation study description

Each of the above described scenarios is investigated based on simulated data over 1000 trials. The following assumptions are made in order to run these simulations:

1. The time to event (PD or death), censoring time and accrual time are all assumed to follow exponential distribution. For all the above scenarios the accrual is assumed to be 8 patients per month.
2. The End of Study is assumed to be at the day of 70^{th} event.

Simulation is performed in the following steps:

Step 1:

Based on the assumed distributions of time to event and accrual time, PFS data are simulated for patients in the PDR001 arm and SOC arm (randomization ratio 2:1) sequentially until the required number of events (70 events) is reached.

Step 2:

The simulated data is then transformed as the number of patients at risk and number of events in different time intervals for each treatment group similar to historical data. But the total number of interval in the simulation depends on maximum event/censored time.

Step 3:

As mathematical closed forms are not tractable, hence, posterior distributions for the log (HR) from Bayesian Cox PH model are computed via MCMC combining the mixture MAP prior obtained from the historical data together with the simulated transformed data.

Step 4:

Claim positive result for the Bayesian method if Posterior median HR < 0.7 and Prob (HR>1)< 0.1.

Step 5:

Repeat step 1-4 for 1000 trials. Calculate the rate of positive results for both the Bayesian design and the frequentist approach.

14.3.2.3 Simulation study results

Table 14-10 shows the operating characteristics for the six scenarios.

Results from Table 14-10 shows that the Bayesian Cox PH model using Mixture prior yields reasonable 1-sided type I error (0.081-0.191) and power (0.7-0.92) under different scenarios in alignment between current and historical data.

Table 14-10 Operating characteristics for the six scenarios

Scenario	Median PFS SOC Arm (months)	Median PFS PDR001 Arm (months)	HR	Type I error/Power	Estimated HR
1	5.5	5.5	1	0.081	0.973
2	5.5	10.0	0.55	0.922	0.509
3	5.5	8.2	0.67	0.727	0.629
4	7.5	7.5	1	0.191	0.894
5	7.5	13.6	0.55	0.911	0.482
6	7.5	12.9	0.67	0.728	0.586

14.3.3 References (available upon request)

Chua DT, Sham JS, Au GK (2003) A phase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. Oral Oncol; 39(4):361-6.

Foo KF, Tan EH, Leong SS, et al (2002) Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. Ann Oncol.; 13(1):150-6.

Krams M, Lees KR, Berry DA (2005) The past is the future: Innovative designs in acute stroke therapy trials, Stroke. 36(6):1341-7.

Neuenschwander B, Capkun-Niggli G, Branson M, et al (2010) Summarizing historical information on controls in clinical trials. Clin Trials; 7:5-18.

Ngeow J, Lim WT, Leong SS, et al (2011) Docetaxel is effective in heavily pretreated patients with disseminated nasopharyngeal carcinoma. Ann Oncol.; 22(3):718-22.

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Wang CC, Chang JY, Liu TW, et al (2006) Phase II study of gemcitabine plus vinorelbine in the treatment of cisplatin-resistant nasopharyngeal carcinoma. Head Neck; 28(1):74-80.

Zhang L, Zhang Y, Huang PY, et al (2008) Phase II clinical study of gemcitabine in the treatment of patients with advanced nasopharyngeal carcinoma after the failure of platinum-based chemotherapy. Cancer Chemother Pharmacol.; 61(1):33-8.

14.4 Appendix 4: Management algorithms

These general guidelines for management of toxicities (Postow 2015-supplementary appendix) constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology (I-O) agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

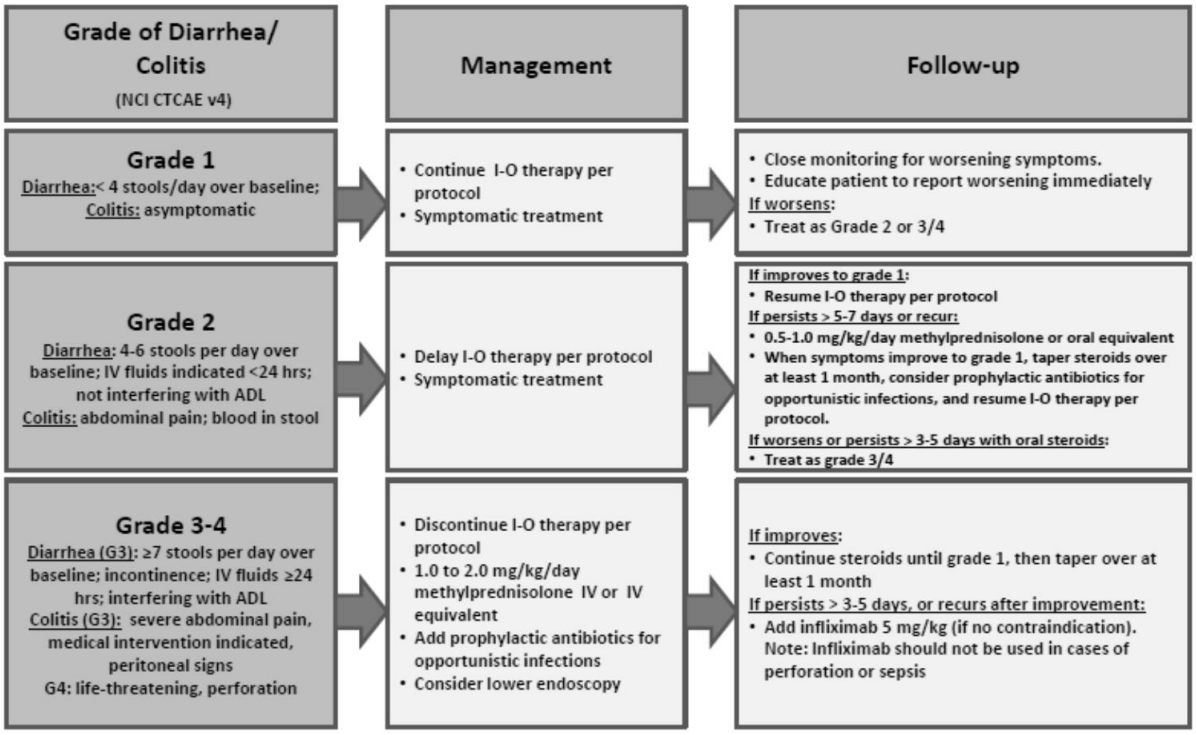
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

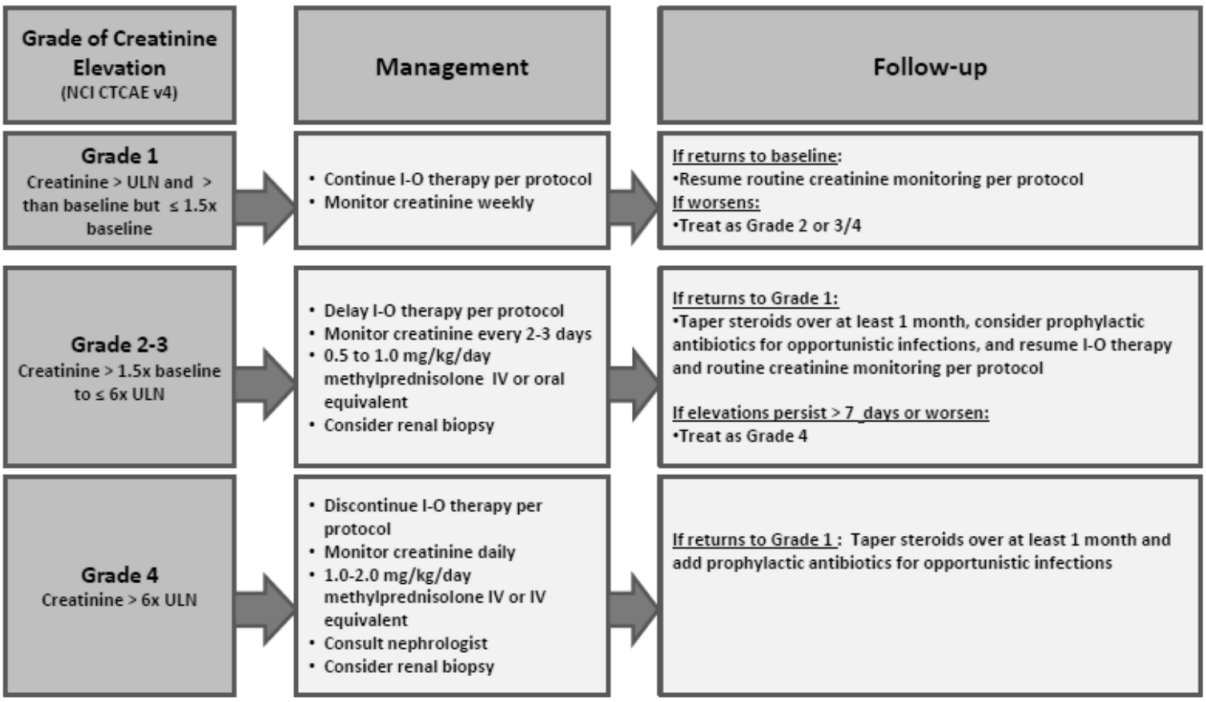
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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.

Renal Adverse Event Management Algorithm

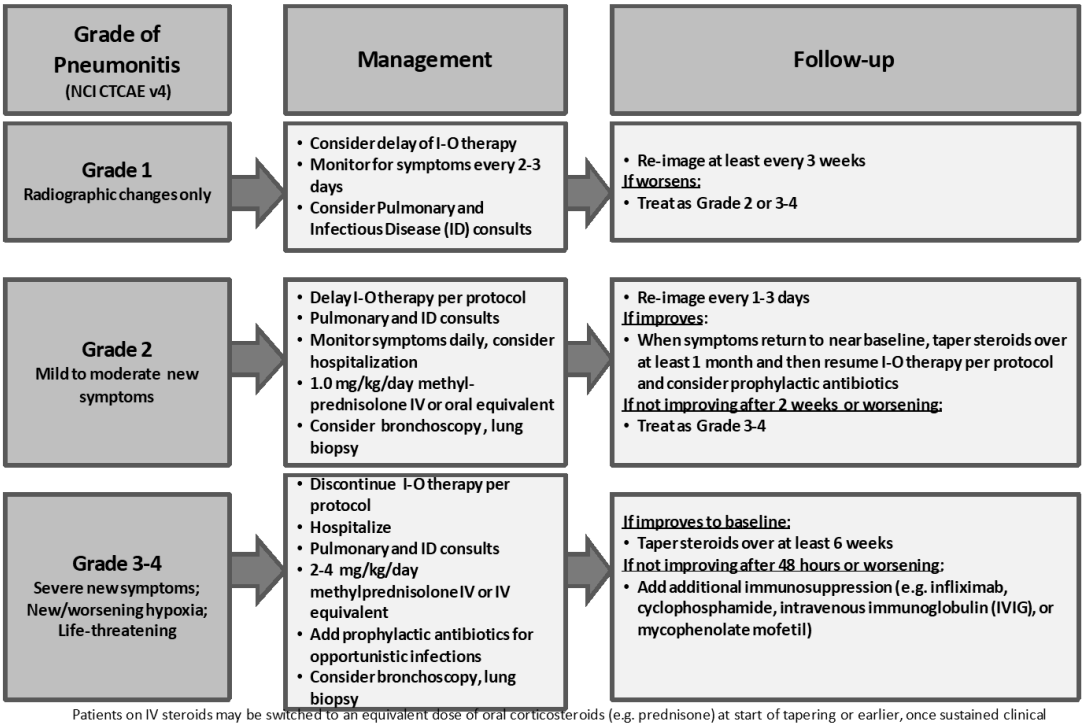
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

Pulmonary Adverse Event Management Algorithm

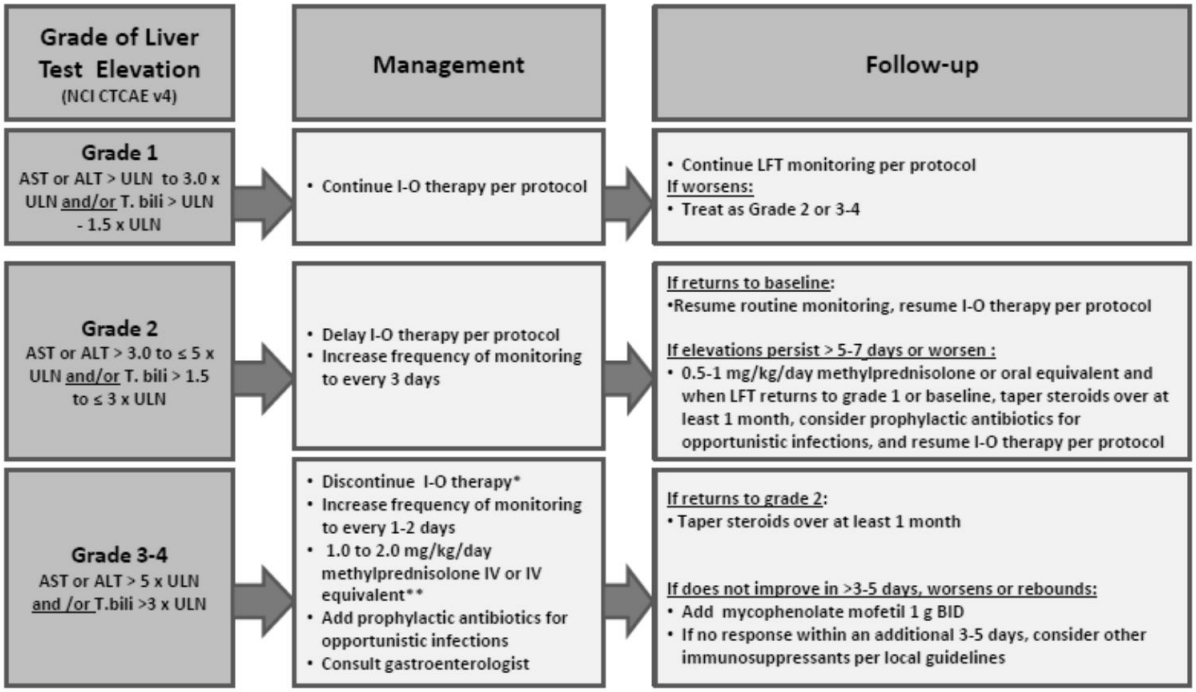
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



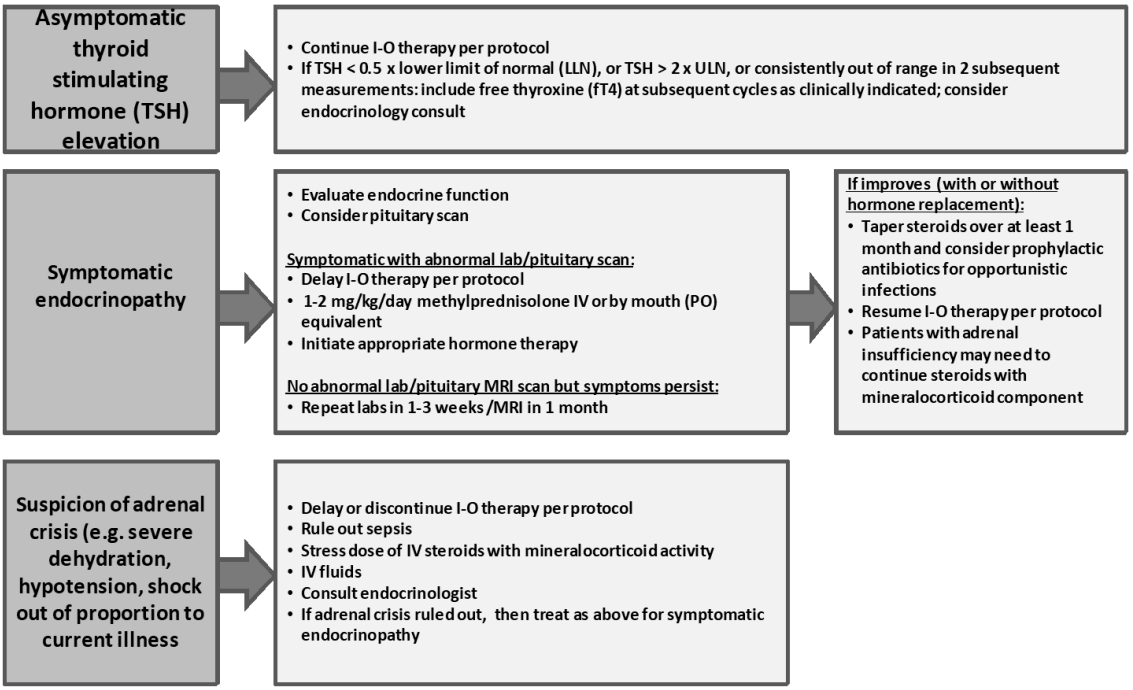
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

Endocrinopathy Management Algorithm

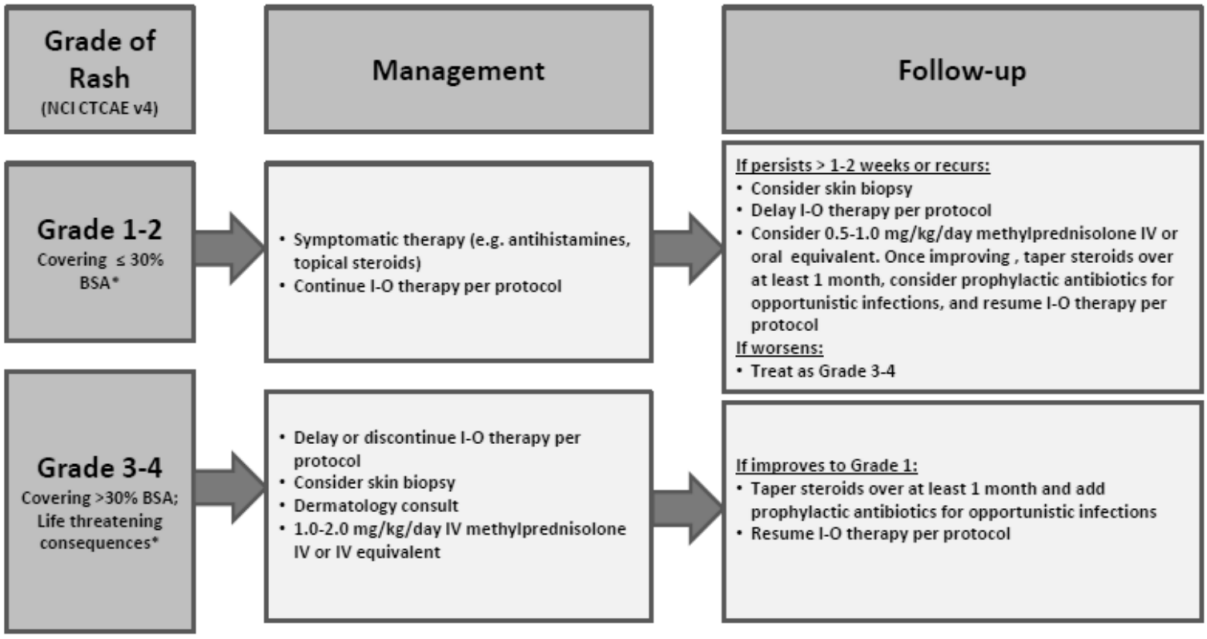
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

Skin Adverse Event Management Algorithm

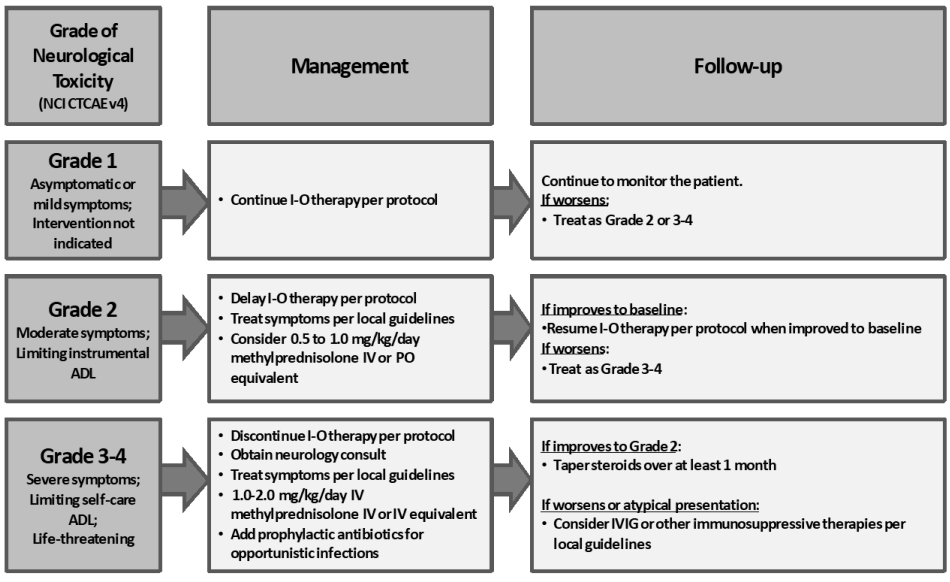
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Neurological Adverse Event Management Algorithm

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



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

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).