NOVARTIS

Clinical Development

PDR001 (Spartalizumab)

Oncology Clinical Protocol CPDR001E2201 / NCT02955069

An open label phase II study to evaluate the efficacy and safety of PDR001 in patients with advanced or metastatic, well-differentiated, non-functional neuroendocrine tumors of pancreatic, gastrointestinal (GI), or thoracic origin or poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC), that have progressed on prior treatment

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List of abbreviations

ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BIRC	Blinded Independent Review Committee
BUN	Blood Urea Nitrogen
CgA	Chromogranin A
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central nervous system
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
Ctrough	Trough plasma concentration
DCR	Disease Control Rate
DILI	Drug-induced liver injury
DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer's core quality of life questionnaire
EOT	End of Treatment
EQ-5D-5L	EuroQol 5 Dimension questionnaire
FAS	Full Analysis Set
FPFV	First patient first visit
GEP-NET	Gastroenteropancreatic NET
GEP-NEC	Gastroenteropancreatic neuroendocrine carcinoma
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
HRQoL	Health-related quality of life
IA	Interim Analysis
IASLC	International Association for the Study of Lung Cancer
i.v.	intravenous(ly)
IEC	Independent Ethics Committee
IG	Immunogenicity
IHC	Immunohistochemistry
IFN-γ	interferon-gamma
IL-1	Interleukin-1

[redacted]

IL-6	Interleukin-6
INR	International normalized ratio
irAE	Immune-related adverse events
irDoR	Immune-related Duration of Response
irORR	Immune-related Overall Response Rate
irPFS	Immune-related Progression Free Survival
IRB	Institutional Review Board
irRECIST	Immune-related RECIST
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
LAR	Long-Acting Release
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LPFT	Last patient first treatment
LPLV	Last patient last visit
mAb(s)	monoclonal Antibody(ies)
mo	Month/s
mOS	median overall survival
mPFS	median PFS
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NET	Neuroendocrine Tumor
NSE	Neuron Specific Enolase
ORR	Overall Response Rate
OS	Overall Survival
[redacted]	[redacted]
PD	Progressive disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS	Progression Free Survival
PK	Pharmacokinetics
PNET	Pancreatic NET
PPoS	predictive probability of success
PR	Partial response
PRO	Patient-reported outcomes
PRRT	Peptide Radionuclide Receptor Therapy
PT	Prothrombin time
QoL	Quality of Life
QTcF	Corrected QT interval based on Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	Relapse-Free-Survival
RP2D	Recommended phase two dose
R Value	ALT/ALP in x ULN
SAE	Serious Adverse Event
SAP	The Statistical Analysis Plan (SAP) is a regulatory document which provides evidence of preplanned analyses
SC	Steering Committee
SD	Stable Disease
SOP	Standard Operating Procedure
SSA	Somatostatin Analogs

[redacted]

TBIL	Total bilirubin
TIL(s)	Tumor Infiltrating Lymphocyte(s)
TNF-α	Tumor necrosis factor alpha
Treg	regulatory T cells
TSH	Thyroid Stimulation Hormone
TTP	Time to progression
TTR	Time To Response
WOCBP	Women of childbearing potential

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient
Blinded Independent Review Committee	A third party review committee which provides an independent, unbiased and impartial assessment of disease response or progression for each patient enrolled in a clinical trial. The BIRC is blinded to all sites and subject identifying information as well as the results of the local assessment. Independent reviews of images and/or clinical data are performed independently of and separate from the reviews performed by investigators at clinical sites. Assessments from site investigators or other third party reviewers will not be provided to the image vendor since these evaluations may bias the image vendors' reviewers' assessments.
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Personal Data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Subject Number (Subject 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.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient 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 interruption	Includes any delay or withholding of study treatment for any reason as well as an interruption during an infusion of study treatment for any reason
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Amendment 3 (24-May-2018)

Amendment rationale

Recruitment into Part 1 of the study completed on 20-Sep-2017 with 116 patients (of approximately 110 planned) enrolled. A planned interim analysis as well as an additional efficacy analysis (to inform decision to start part 2) were performed with data cut-off dates of 29-Nov-2017 and 09-Feb-2018, respectively. The key efficacy and safety results of the two analyses are summarized in Section 1.2.1.2. No new safety signals were identified in the interim analysis. As of 15-May-2018, recruitment into Part 2 has not opened and no patients were enrolled into Part 2.

The major rationale for protocol amendment 3 is to remove the possibility to expand the study to Part 2 when at least 20% overall response rate (ORR) per RECIST 1.1 by central radiology review is observed in any of the cohorts of the well-differentiated NET group. While the results of the additional efficacy analysis (Section 1.2.1.2) demonstrated an ORR of 20% in the thoracic cohort of the well-differentiated NET group and met the criterion for starting Part 2, no overwhelming supportive evidence of strong efficacy was observed on other endpoints. Moreover, all other cohorts showed ORR below 10%. Based on this, there was a change in the clinical development strategy for PDR001, which will no longer be developed as a single agent immunotherapy in NET, and the study will not be expanded into Part 2. Importantly, this change is not due to safety concerns.

Due to revoking Part 2, no further patient will be enrolled in the study and the primary analysis will provide results for all enrolled patients. Consequently, the following modifications will be implemented **after the primary analysis cut-off date (10-Aug-2018):**

- Tumor response assessments will be performed according to local or institutional standards of care and when clinically indicated.
- Removal of tumor response assessments by the Blinded Independent Review Committee (BIRC); tumor response will be assessed locally.
- Removal of post-treatment efficacy follow-up. There will be no change to the safety follow-up or survival follow-up.
- Removal of the Patient Reported Outcomes (PRO) data collection.

Additional changes to the protocol include:

- Following the release of Investigator Brochure Edition 7.1, changes to the Risks and Benefit section have been implemented and the contraception requirement for male participants has been updated. Condom use for males receiving monoclonal antibodies is no longer required since monoclonal antibodies are not genotoxic due to their high molecular weight, and are not expected to interact with DNA. In addition, they have a low distribution to the semen, a relatively small volume of semen is delivered to the vagina, and there is very low absorption. Fetal harm from semen delivery is therefore biologically implausible.
- Withdrawal of consent language was updated to reflect the European Economic Area General Data Protection Regulation (GDPR) requirements.
- Editorial changes and text corrections were made for clarification, where required.

[redacted]

Changes to the protocol

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

The following sections were changed:

Section 1.1.1: updated to reflect FDA approval of 177 Lu-Dotatate for treatment of somatostatin receptor positive for GEP-NETsSection 1.2.1.2: added study results of Interim Analysis

Sections 2.2: deleted Part 2 expansion

Section 3: deleted objectives for Part 2 expansion

Section 4.1: deleted Part 2 expansion and updated treatment duration for patients ongoing after primary analysis cutoff date

Figure 4-1: deleted Part 2 expansion

Section 4.1.1: updated section to reflect that post-treatment efficacy follow-up, ePRO collection and central radiology review will no longer be performed after primary analysis cutoff date

Sections 4.2 and 4.3: deleted Part 2 expansion

Section 5: deleted inclusion criterion 13 due to removal of Part 2 and exclusion criterion 25 as male contraception is no longer required

Sections 6.1, 6.1.1 and 6.6.2: deleted introduction of the PDR001 liquid formulation due to the removal of Part 2 (liquid formulation was supposed to be introduced in Part 2)

Section 6.1.5: updated treatment duration for patients ongoing after primary analysis cutoff date

Section 7: updated Visit Schedule and Assessment Table 7-1 with change in efficacy assessments frequency for ongoing patients and discontinuation of post treatment efficacy follow-up, central radiology review after primary analysis cutoff date and clarified that PK/IG samples will not be collected after primary analysis cutoff date unless if requested by the investigator . There are no change in assessment frequency prior to primary analysis cutoff date.

Section 7.1.5: updated treatment duration for patients ongoing after primary analysis cutoff date

Section 7.1.6: updated as per the European Economic Area General Data Protection Regulation (GDPR) requirements

Section 7.1.7: updated to confirm that there is no change in the safety evaluations after the primary analysis cutoff date

Section 7.1.8: updated section to reflect discontinuation of post treatment efficacy follow-up after primary analysis cutoff date

Section 7.2.1, 7.2.3, 7.2.4 and 7.2.5: updated sections to reflect change in efficacy assessments frequency for ongoing patients and discontinuation of post treatment efficacy follow-up, and central radiology review including expedited review after primary analysis cutoff date

Section 7.2.7: highlighted and clarification added that no additional PK and IG samples will be collected for the patients still ongoing on the study, unless requested by the Investigator, after primary analysis cutoff.

[redacted]

Section 7.2.10: updated section to reflect discontinuation of ePRO collection after primary analysis cutoff date

Section 10: updated to remove the possiblity to expand the study to Part 2

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.

Summary of previous amendments

Amendment 2 (12-Jan-2018)

Amendment rationale

The first patient signed the informed consent on 14 February 2017. As of 05 January 2018, 95 patients with well-differentiated non-functional NET and 21 patients with poorly differentiated GEP-NEC have been treated with at least one dose of PDR001. The enrollment in part 1 is completed and the study is currently ongoing.

Amendment 2 includes the following modifications:

- Inclusion of Part 2 (Expansion part) aiming to further characterize the efficacy and safety of PDR001 single agent in any of the well-differentiated NET cohorts if antitumor activity is observed in Part 1. Each of the well-differentiated cohorts (GI, thoracic, pancreatic) will enroll additional 60 patients if we observe at least 20% ORR per RECIST 1.1 and central radiology review in the corresponding cohort.
- Possibility to implement the PDR001 liquid formulation for patients treated in Study Part 2 (expansion part).Addition of an inclusion criterion regarding life expectancy of at least 3 months for patients treated in Study Part 2. This would decrease the occurrence of deaths during the screening period and before the first tumor assessment scheduled 8 weeks after the first treatment dose.

Rationale for possible expansion of Well-differentiated NET:

Well-differentiated, non-functional NETs of the thorax, gastrointestinal tract and pancreas are rare and heterogeneous, clinically important group of neosplasms with a different clinical management and available therapeutic options. The management of patients with metastatic NETs includes systemic and biological treatment strategies such as molecular targeted therapies with everolimus and sunitinib, PRRT and chemotherapy. PD-L1 expression emerged as a potential prognostic factor for survival in NET; showing that patients with PD-L1 negative tumors experience a longer survival as compared to PD-L1 positive however limited data is available regarding the treatment effect of checkpoint inhibitors in NET (Kim 2016; Fan 2016;

[redacted]

Mehnert 2017). There are no available treatment options with proven efficacy post everolimus failure and a limited number of agents approved specifically in NET of GI and lung origins, representing an unmet need. Considering the high level of heterogeneity between different NET origins, if an activity signal is observed in any of the 3 cohorts, an expansion in the sample size will be performed to better assess the efficacy of PDR001 in that specific NET subgroup.

Changes to the protocol

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

- Section 1.1.1: updated treatment options with most updated data
- Section 2.2: added part 2 (expansion) for well-differentiated cohort
- Section 3: added primary and key secondary objectives [redacted] for part 2
- Section 4.1: added definition of part 2 expansion
- Figure 4-1: updated study design for part 2
- Section 4.1.1: clarified 150-day safety follow-up schedule
- Section 4.3: updated definition of end of study
- Section 5.2: Added new Inclusion criterion 13 for patients enrolled in Part 2: life expectancy of at least 3 months
- Section 6.1: added new formulation of study treatment (PDR001 100 mg / 4 mL concentrate for solution for infusion)
- Section 7.1: added time window for EOT visit
- Section 7.2.1: added information about cytology
- Section 10: updated to reflect the possibility to expand and analyze well-differentiated NET cohorts
- Section 13: added new references
- Other minor clarifications and editorial changes.

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[redacted]

Amendment 1 (27-Apr-2017)

Amendment rationale

The first patient signed the informed consent on February 14, 2017. As of 24-Apr-2017, 7 patients have been treated with at least one dose of PDR001.

Amendment 1 includes the following modifications:

- Adding a group of approximately 20 patients with advanced or metastatic, poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC). This cohort is added because of the following reasons: 1) biological rationale supporting the potential efficacy of immunotherapy; 2) currently there is no approved treatment and no consensus on the standard of care upon progression on 1st line chemotherapy.
- Removing the possibility of stopping the study early for futility at the time of the protocol defined interim analysis. By the time of the planned interim analysis, enrollment is expected to be completed. A formal interim analysis of preliminary efficacy and safety data will be kept, but the study will not be stopped for efficacy reasons regardless of efficacy results and the study will continue until mature data for all patients become available.
- Modifying the inclusion criterion 4 and adding exclusion criterion 27. "No history of carcinoid syndrome" was removed from this inclusion criterion since this condition may be present during the course of the disease but may have resolved with appropriate treatment and therefore not present at the time of enrollment. A period of 3 months without any evidence of carcinoid symptoms and somatostatin analogs treatment has been defined prior to study entry.
- Modifying the inclusion criterion 9. The tumor sample should be taken within 6 months but not more than 24 months (instead of 12 months) prior to start of study treatment. Extending the collection period from a maximum of 12 months to 24 months improves recruitment [redacted].
- Adding exclusion criterion 26. Interstitial lung disease was observed in ongoing PDR001 studies.
- Removing the maximum treatment duration of 24 months. The limit on treatment duration is removed to provide the option of continuing study treatment for those patients who present clinical benefit and have not progressed during the first 24 months of treatment and still fulfils the criteria to continue study treatment.
- Extending the treatment window from +/- 4 days to +/- 7 days based on investigators' feedback that more time is required between routine blood collection and start of study treatment.
- Modifying the exclusion criteria 13 for QTcF from > 450 to > 480 msec on screening ECG or congenital long QT syndrome because monoclonal antibodies such as PDR001 have low potential for QT prolongation.
- Updating safety information according to release of Investigator Brochure edition 6
- Clarifying the definition of on-treatment period for safety analysis to align reporting with data collection. Main safety analysis will be performed based on data collected up to 30 [redacted]

days after discontinuation of study treatment. Additional analyses will be performed to report data up to 150 days after discontinuation of PDR001.

- Other minor clarifications and editorial changes.

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.

- Title: updated to include poorly-differentiated GEP-NEC patients
- Section 1.1: added additional details of neuroendocrine tumor classification
- Section 1.1.1: added treatment strategies for poorly-differentiated GEP-NEC
- Section 1.2.1.2: deleted details of six safety notifications and replaced with an overview of new safety information from IB version 6
- Section 2: added rationale for including poorly-differentiated GEP-NEC group
- Section 3: modified objectives to include poorly-differentiated GEP-NEC group
- Section 4: added poorly-differentiated GEP-NEC group to study design
- Section 4.2: deleted futility interim analysis and replaced with interim analysis
- Section 4.3: updated end of study definition
- Section 4.4: updated early study termination language
- Section 5.1: added poorly-differentiated GEP-NEC group to patient population
- Section 5.2: modified criteria as below:
  - inclusion criterion 3: included poorly-differentiated GEP-NEC group
  - inclusion criterion 4: deleted “no history of carcinoid syndrome” and added time window for active symptoms
  - inclusion criterion 5: added prior treatment for poorly-differentiated GEP-NEC group
  - inclusion criterion 6: added radiological documentation for poorly-differentiated GEP-NEC group
  - inclusion criterion 9: extended time window for tumor sample collection from 1 year to 24 months and added specific criterion for poorly-differentiated GEP-NEC
- Section 5.3: modified criteria as below:
  - exclusion criterion 1: updated to exclude well-differentiated, grade 3 neuroendocrine tumors; poorly differentiated neuroendocrine carcinoma of any origin (other than GEP-NEC); including NEC of unknown origin, adenocarcinoid, and goblet cell carcinoid.
  - exclusion criteria 6 and 11: deleted these criteria
  - exclusion criterion 13: updated QTcF to > 480 msec
  - exclusion criterion 14: updated
  - exclusion criterion 26: added criterion to exclude patients with known history or current interstitial lung disease or non-infections pneumonitis
  - exclusion criterion 27: added criterion to exclude patients using somatostatin analogs or other medications to control active symptoms of carcinoid syndrome.

[redacted]

  - Note: the deletion of exclusion criteria 6 and 11 did not change the numbering of the existing exclusion criteria
- Section 6.1.1: updated dosing window to +/- 7 days and pharmaceutical form
- Sections 6.1.5 and 7.1.4: deleted maximum treatment duration of 24 months
- Section 6.1.5.1: clarified absence of irPD criteria
- Section 6.3.1.2:
  - added other skin events in Table 6-4 and autoimmune diabetes in Table 6-8 with details regarding dose modification and clinical management guidelines
  - deleted example of non-corticosteroid immunosuppressive medication in Table 6-6
- Section 6.4.3: updated prohibited medication list
- Section 6.5.2: updated to include poorly-differentiated GEP-NEC group
- Section 6.6: clarified post infusion monitoring
- Section 7.1: changes are described below:
  - updated time windows for scans, ePRO and Day 1 of subsequent cycles
  - clarified suspected SAE collection up to end of survival follow-up in Table 7-1
  - added tumor characteristic collection as part of proliferative assessment in Table 7-1
- Section 7.1.2: added poorly-differentiated GEP-NEC group and collection of necrosis from pathology report
- Section 7.1.5: deleted end of treatment reason “completed”
- Section 7.2.4: clarified expedited review requirements
- Section 7.2.6.4: added ECOG performance status scale table
- Section 7.2.6.5: added new section to include details of change in functional status of carcinoid syndrome
- Section 7.2.6.6.4: added new section for coagulation
- Section 7.2.6.6.7: added new section for CgA and NSE
- Section 7.2.6.7.1: updated Table 7-6
- Section 7.2.7: updated Table 7-7 (dose reference ID) and clarified collection timing for pre-dose sample and end of infusion sample collection
- Section 7.2.8: updated Table 7-8: clarified tumor collection timepoints for well-differentiated NET and GEP-NEC and added a new archival tumor sample collection (older than 24 months)
- Sections 8.2.2 and 8.4: updated to reflect new name for Novartis safety group
- Section 10: reflected changes to statistical considerations for including poorly-differentiated GEP-NEC group and removal of the possibility for early stopping due to futility at the interim analysis
- Section 13: added new references
- Section 14: updated appendix 14.2 for consistency with Novartis guidelines

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[redacted]

Protocol summary:

Title	An open label phase II study to evaluate the efficacy and safety of PDR001 in patients with advanced or metastatic, well-differentiated, non-functional neuroendocrine tumors of pancreatic, gastrointestinal (GI), or thoracic origin or poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC) that have progressed on prior treatment
Brief title	Study of efficacy and safety of PDR001 in patients with advanced or metastatic, well-differentiated, non-functional neuroendocrine tumors of pancreatic, gastrointestinal (GI), or thoracic origin, or poorly-differentiated GEP-NEC
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	● Although many advances with checkpoint inhibitors have been made in other tumor types, the data generated in NETs is limited with no clinical experience available to date. Recent correlative studies conducted in NETs have assessed the expression of PD-L1 and correlated tumor differentiation with poor clinical outcome. ● Tumor-infiltrating lymphocytes (TILs) have been shown to predict survival in numerous malignancies. A robust T cell infiltration is associated with improved RFS following resection of intermediate-grade NETs, whereas the presence of a tumor environment rich in Tregs correlated with shorter OS after treatment. These findings suggest that the immune-modulation of the phenotype of T cells may play a role in clinical outcome. ● Clinical data available from one patient with histologically confirmed metastatic atypical pulmonary carcinoid treated in the ongoing phase I study with PDR001 in solid advanced tumors [CPDR001X2101] showed an immune-related partial response with dramatic resolution of multiple liver and pleural metastases. Patient has been on therapy for nine months, and at the last tumor imaging assessment a sustained partial response according to RECIST 1.1 criteria was observed with sustained regression in all areas of tumor.
Primary Objective and Key Secondary Objective	**Primary objective:** ● To estimate the antitumor activity (assessed as ORR per RECIST 1.1) of PDR001 as a single agent in the well-differentiated NET and the poorly-differentiated GEP-NEC groups. **Key secondary objective:** ● To estimate efficacy (DoR per RECIST 1.1) of PDR001 in the well-differentiated NET and poorly-differentiated GEP-NEC groups.
Secondary Objectives	**Other secondary** ● To assess the safety and tolerability of PDR001 in each group and in the overall study population. ● To evaluate in each group additional efficacy parameters per RECIST 1.1 and per Immune Response Criteria irRECIST as well as 1-year and 2-year OS rate ● To evaluate biochemical response to treatment (based on CgA and NSE) in each group ● To characterize the pharmacokinetics of PDR001 with 400 mg flat dose Q4W in each group ● To characterize patient's health-related quality of life with PDR001 in each group ● To evaluate the prevalence and incidence of immunogenicity in each group
Study design	This is a phase II, single-arm, open-label, multi-center study.
Population	Patients with unresectable advanced or metastatic, well-differentiated, non-functional NETs of GI, pancreatic or thoracic origin, or poorly-differentiated GEP-NEC who have progressed on or after prior available treatments. ● A total of approximately 90 patients will be enrolled in the well-differentiated group, with approximately 30 patients enrolled in each cohort based on tumor origin. Approximately 20 patients will be enrolled in the poorly-differentiated GEP-NEC group, for a total number of approximately 110 patients.

[redacted]

Key Inclusion criteria	● Pathologically confirmed, advanced (unresectable or metastatic): ● Well-differentiated (G1/2) based on local pathology report, non-functional neuroendocrine tumor of GI, pancreatic or thoracic (including lung and thymus) origin. ● Poorly-differentiated GEP-NEC based on local pathology report ● No active symptoms related to carcinoid syndrome during the last 3 months prior to start of study treatment. ● Patients must have received prior treatment for advanced disease: ● **Well-differentiated NET group:** ● Thoracic (lung and thymus origin) cohort: ● Thymus origin: at least one prior systemic therapy according to investigator's choice. ● Lung origin: at least one prior systemic therapy is required, which must include everolimus. ● GI cohort: at least two prior systemic regimens, which must include everolimus. Prior systemic therapies may include: somatostatin analogs, PRRT, and/or chemotherapy. ● PNET cohort: at least two prior systemic regimens, which must include everolimus or sunitinib. Prior systemic therapies may include: somatostatin analogs, PRRT, and/or chemotherapy. Note: For well-differentiated NET, prior treatment with interferon alpha is allowed provided that it is not the last treatment received prior to study entry ● **Poorly-differentiated GEP-NEC group:** At least one prior chemotherapy regimen according to Investigator's choice. ● Tumor biopsy material must be provided for all patients [redacted]: ● Well-differentiated (G1/2) NET: Biopsy material must be provided following the diagnosis of metastatic disease. The tumor sample must be collected from a metastatic site not previously irradiated and should preferably be taken within 6 months but not more than 24 months prior to start of study treatment. ● Poorly-differentiated GEP-NEC: Biopsy material must be collected from the primary tumor or from a metastatic site not previously irradiated, taken not more than 24 months prior to start of study treatment. ● Radiological documentation of disease progression: ● Well-differentiated NET group: disease progression while on/or after the last treatment; progression must have been observed within 6 months prior to start of study treatment (i.e. maximum of 24 weeks from documentation of progression until study entry). Disease must show evidence of progression based on scans performed not more than 12 months apart. ● Poorly-differentiated GEP-NEC group: disease progression while on/or after prior treatment ● At least one measurable lesion assessed by CT and/or MRI according to RECIST 1.1. Note: Any lesions which have been subjected to percutaneous therapies or radiotherapy should not be considered measurable, unless the lesion has clearly progressed since the procedure.
Key Exclusion criteria	● Well-differentiated, grade 3 neuroendocrine tumors; poorly differentiated neuroendocrine carcinoma of any origin (other than GEP-NEC) including NEC of unknown origin, adenocarcinoid, and goblet cell carcinoid ● Pretreatment with interferon as last treatment prior to start of study treatment. ● Prior treatment for study indication with: ● Antibodies or immunotherapy within 6 weeks before the first dose of study treatment. ● PRRT administered within 6 months of the first dose. ● Systemic antineoplastic therapy (including cytotoxic chemotherapy, and toxin immune-conjugates) or any experimental therapy within 14 days or 5 half-lives, whichever is longer, before the first dose of study treatment. For cytotoxic agents that

[redacted]

	have major delayed toxicities a washout period of more than 6 weeks is required (examples are nitrosoureas and mitomycin C). ● Tyrosine kinase inhibitors within 14 days or 5 half-lives, whichever is longer, before the first dose of study treatment. ● Prior PD-1- or PD-L1-directed therapy. ● Cryoablation, radiofrequency ablation, or trans-arterial embolization of hepatic metastases within 2 months before the first dose of study treatment. ● History of severe hypersensitivity reactions to other monoclonal antibodies which in the opinion of the investigator may pose an increased risk of a serious infusion reaction. ● Known history or current interstitial lung disease or non-infections pneumonitis. ● Use of somatostatin analogs or any other medications administered to control active symptoms related to carcinoid syndrome during the last 3 months prior to start of study treatment.
Investigational and reference therapy	PDR001 (flat dose, 400mg, Q4w); Drug formulation (PDR001 100 mg powder for solution for infusion)
Efficacy assessments	**Radiological tumor assessments performed (per RECIST 1.1 and irRECIST) <u>before</u> the primary analysis cut-off date (10-Aug-2018):** ● At screening ● Treatment Period: Every 8 weeks from Cycle 1 Day 1 for the first 13 cycles and every 12 weeks from Cycle 13 Day1 thereafter ● EOT: If a scan was not conducted within 30 days prior to end of study treatment ● Efficacy follow-up: Continue same schedule as during treatment period until blinded independent review committee (BIRC) confirmed irRECIST progression **Survival phone calls** Q3 months after safety and efficacy follow up period. **Radiological tumor assessments performed <u>after</u> the primary analysis cut-off date (10-Aug-2018):** ●Treatment Period: Assessments scheduled according to local or institutional standards of care, and when clinically indicated, until locally-determined disease progression (per RECIST 1.1 or irRECIST). All tumor response assessments will be performed by investigator locally and reported in the eCRF. ● EOT: no scan is needed to be perfomed at EOT **Survival phone calls** Q3 months after safety and efficacy (if applicable) follow up period(s).
Safety assessments	● Physical examination ● ECOG Performance status (PS) ● Weight and vital signs ● 12-lead ECGs ● Laboratory assessments, including hematology, chemistry, thyroid function, coagulation, hepatitis testing, urinalysis, and cytokine analysis ● Pregnancy testing for women of child-bearing potential ● Adverse events (AEs), the severity, the relationship to study treatment and the seriousness **There will be no changes in safety assessments after the primary analysis cut-off date (10-Aug-2018).**
Other assessments	**Other assessments performed <u>before</u> the primary analysis cut-off date (10-Aug-2018**): ● Pharmacokinetics (Ctrough) and Immunogenicity (ADA) [redacted] ● Patient reported outcomes assessment by the European Organization for Research and Treatment of Cancer quality of life (EORTC QLQ-C30) and EuroQoL (EQ-5D) questionnaire [redacted]

[redacted]

Data analysis	No formal hypothesis testing will be used for the primary analysis. The primary efficacy variable of the study is overall response rate (ORR), defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR), as per RECIST 1.1 and blinded independent central review. ● Well-differentiated NET Group: The response rate on all patients with 95% two-sided confidence interval (exact method) will be computed. In the absence of an established control treatment, ORR reported in the placebo arms of studies in NET can serve as a reference. A 3% ORR is therefore considered as a reasonable reference while an improvement up to 10% is considered as clinically meaningful in this patient population. The study will be considered a success in this group if both of the following conditions are met: a. a clinically relevant response rate of at least 10% is observed b. 95% two-sided CI for ORR excludes the value 3%. ● Poorly-differentiated GEP-NEC Group: Estimates of the ORR along with 95% confidence intervals will be presented and the interval probabilities for the true ORR lying within the intervals stated below will be assessed: 0 - <3% unacceptable efficacy 3% - <10% limited efficacy 10% - <20% moderate efficacy ≥20% clinically relevant efficacy.
Key words	PDR001, immunotherapy, PNET, GI NET, thoracic NET, GEP-NEC

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Neuroendocrine tumors (NETs) are heterogeneous entities with a pathological interrelation originating from the diffuse neuroendocrine cell system. While NETs are not frequent, their prevalence has been increasing over the last 20 years (Yao 2008). Furthermore, their incidence has also increased, rising to 5 per 100,000 in recent years from 1 per 100,000 in the early 1970s (Dong 2012). However, it is not fully proven that this increase is a result of better recognition of these pathologic entities or rather a true increase of the incidence of the disease. NETs can be further sub classified according to their embryologic origin: hindgut (rectum and distal colon), midgut (proximal large bowel, ileum, appendix and jejunum) and foregut (stomach, duodenum, thymus and lung) (Dong 2012). The majority of NETs are located in the gastro-intestinal (GI) tract (more than 60% of all NETs and they are also known as gastroenteropancreatic NETs [GEP-NETs]) or in the lungs (almost 30%). The most frequent sites of primary GEP-NET are the: small intestine (28%), appendix (20%), pancreas (16%), rectum (15%), colon (13%) and stomach (9%). Distant metastases at diagnosis are relatively rare for primary tumors of the appendix (3%), rectum (6%) and stomach (15%); whereas the metastases are more frequent for small intestine (45%), pancreas (42%) and colon (40%) (Frilling 2014).

Neuroendocrine tumors are classified into 3 broad histologic categories based on tumor differentiation: well-differentiated (G1); intermediate-grade (G2); and poorly-differentiated, high grade tumors (NCCN Guidelines V1.2017). Neuroendocrine carcinomas represent approximately only 15% of all NETs (Yao 2008). Tumor differentiation and tumor grade often correlate with mitotic count and Ki-67 proliferation index (Kloppel 2010; Rekhtman 2010). The gastroenteropancreatic (GEP) tract is the most common site of extrapulmonary NET accounting for 35% to 55% of all neuroendocrine tumors originating from the lung (Garcia Carbonero 2016).

The classification of neuroendocrine tumors in functioning or non-functioning is based on the presence of symptoms that accompany these syndromes secondary to the secretion of hormones, neuropeptides, and/ or neurotransmitters (functioning tumors). Non-functioning tumors are considered to be neoplasms of neuroendocrine differentiation that are not associated with symptoms attributed to the hypersecretion of metabolically active substances. Presentation of non-functional tumors is either due to an incidental finding or a tumor mass effect (Gut 2015). Well-differentiated NETs are characterized by an indolent course; however, curative surgery is often not possible because the majority of patients present with metastatic disease at the time of diagnosis, with regional or distant tumor spread seen in 50% of patients (Yao et al 2008). Poorly-differentiated neuroendocrine carcinomas are characterized by a high proclivity to metastatic dissemination even in patients with localized tumors (Strosberg 2010). Approximately two thirds of patients present with advanced disease dominated by site-specific tumor-derived symptoms and a syndrome characteristic of advanced cancer (anorexia, weight loss and fatigue) (Strosberg 2010).

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1.1.1 Current treatment options

In patients with well-differentiated G1 or G2 inoperable NET, the treatment goal is to control secretory symptoms (if the tumor is functional), to control tumor growth, and to prolong survival. Biotherapy with somatostatin analogs (SSAs) remains the mainstay of symptomatic therapy as well as an active treatment to control disease burden in well differentiated NET of lung, GI or pancreatic origin (NCCN Guidelines v13 2015; Igarashi 2015; Noel-Savina 2013).

Specifically with regards to gastrointestinal NET, different studies have assessed SSA treatment demonstrating superiority versus placebo:

- PROMID study included treatment-naive patients with metastatic midgut NET; results showed that octreotide LAR (long-acting release) increased time to tumor progression (TTP) when compared to placebo from 6 months to 14.3 months (p=0.000072) (Rinke 2009).
- CLARINET study included patients with advanced, well or moderately differentiated, nonfunctioning, non-progressing GEP-NET; results showed that lanreotide treatment was associated with significantly prolonged median PFS (mPFS) when compared to placebo (not reached vs. 18.0 months, p<0.001) (Caplin 2014).

The phase III NETTER-1 study confirmed the efficacy of peptide radionuclide receptor therapy (PRRT) in patients with well-differentiated midgut NETs after failure of octreotide treatment. This study evaluated 177Lu-DOTATATE plus octreotide LAR vs. octreotide LAR. The mPFS was 8.4 months with octreotide LAR and the median PFS was not reached with 177Lu-DOTATATE (HR = 0.21; P < .0001). The estimated rate of PFS at month 20 was 65.2% (95% CI, 50.0 to 76.8) in the 177Lu-DOTATATE group and 10.8% (95% CI, 3.5 to 23.0) in the control group. Tumor response rate was 3% and 18.8% with octreotide LAR and 177Lu-DOTATATE, respectively (Strosberg 2016, Strosberg 2017). In Sep-2017, 177Lu-DOTATATE received approval in the EU for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults. In Feb-2018 177Lu-DOTATATE received FDA approval for the treatment of somatostatin receptor-positive GEP-NETs, including foregut, midgut, and hindgut neuroendocrine tumors in adults.

Limited antineoplastic therapy options are currently available for patients with progressive metastatic NET of GI and lung origin:

- RADIANT-2 study included patients with advanced functional NET and assessed everolimus-octreotide vs. placebo-octreotide. Results showed a mPFS of 16.4 months (95% CI 13.7–21.2) in the experimental arm vs. 11.3 (8.4–14.6) months in the placebo arm (HR 0.77, 95% CI 0.59–1·00; p=0.026) (Pavel 2011).
- Cytotoxic therapy appears to provide a modest benefit. Although different agents have been evaluated (including capecitabine, temozolamide, streptozocin, doxorubicin), response rates are generally low and no PFS benefit have been clearly demonstrated (NCCN guidelines 2015).
- RADIANT-4 study included patients with advanced, progressive non-functional NET of GI or lung origin. Everolimus demonstrated superiority over placebo in terms of PFS showing a 52% relative risk reduction of progression/death in favor of everolimus (HR: 0.48; 95% CI: 0.35, 0.67) (p<0.001) (Yao 2016). Based on these results, submissions

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worldwide have thus far led to marketing authorization of everolimus in progressive, nonfunctional NET of GI or lung origin in over 41 countries including the US, EU, Canada, and Japan.

The systemic treatment options for non-functional advanced pancreatic NET (PNET) include chemotherapy, somatostatin analogs and targeted agents such as everolimus and sunitinib. Both targeted agents, sunitinib and everolimus, are approved by health authorities worldwide for the treatment of advanced PNET based on the pivotal studies described below:

- RADIANT-3 study included patients with advanced and progressive PNET and assessed everolimus vs. placebo (Yao 2011). The study results showed that mPFS was 11.0 months with everolimus as compared with 4.6 months with placebo (HR=0.35; P<0.001). Subset analyses of RADIANT-3 showed that the PFS effect of everolimus was independent of prior or concurrent SSA therapy or chemotherapy.
- A randomized phase III study evaluated sunitinib in patients with progressive metastatic PNET. The study was stopped before the predefined analysis; the investigator-assessed mPFS for sunitinib arm was 11.4 months compared to 5.5 months in the placebo arm, resulting in a HR of 0.42 (p=0.0001) (Raymond 2011).
- Furthermore, cytotoxic therapy (including streptozocin, temozolamide, doxorubicin, dacarbazine) has been assessed in a number of regimens in PNET yielding response rates in the range of 8%-39% with limited long-term disease control. As of today, there is no panel consensus on which cytotoxic regimen is preferred (NCCN 2015). Streptozocin is the only FDA-approved agent among the cytotoxic agents for use in patients with advanced PNET.

Recently, the Keynote 028 study reported results of pre-treated patients with PD-L1-positive, advanced carcinoid (=25) or PNET (=16) treated with pembrolizumab as single agent. The study results showed an ORR of 12% and 6% in carcinoid group and PNET group, respectively (no Complete Response was observed). The majority of patients have stable disease as best overall response, in 60% and 88% in carcinoid group and PNET group, respectively. The duration of disease stabilization was above 6 months in 32% of patients with carcinoid tumors and 31% of patients with PNET. The mPFS in carcinoid group was 5.6 months (95% CI, 3.5 to 10.7) and in PNET group was 4.5 months (95% CI, 3.6 to 8.3); the mOS observed in both cohorts was 21 months (Mehnert 2017).

Table 1-1 provides an overview of the clinical experience summarized in literature of various therapies in NET.

Table 1-1 Clinical Experience in NET – Literature review of clinical studies

Study	Treatment	Population	ORR	PFS/TTP	OS
Ph II PROMID study (n=90) (Rinke 2009)	Octreotide LAR vs. Placebo (1:1)	G1/2 Midgut	No ORR SD: 66.7%	mPFS: LAR: 14.3 mo Placebo: 6 mo	HR: 0.81 at 84 mo
Ph III CLARINET study (n=204) (Caplin 2014)	Lanreotide vs. Placebo	Advanced, well-mod. differentiated G1/2 NET (GI, pancreas, unknown origin)	NR*	mPFS: Lanreotide: not reached Placebo:18 mo	Cross-over (difficult assessment), not different between groups

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Study	Treatment	Population	ORR	PFS/TTP	OS
Ph III RADIANT-2 study (n=429) (Pavel 2011)	Everolimus +Octreotide vs. Placebo-Octreotide	Functional NET (GI, lung, pancreas). Low/ intermediate grade (24% functional)	Everolimus-Octreotide: 2.3% Placebo-O: 1.9%	mPFS: Everolimus-Octreotide: 16.4 mo Placebo: 11.3 mo	NR
Ph III RADIANT-4 Study (n=302) (Yao 2016)	Everolimus vs. Placebo	NET GI or lung origin G1/2 non-functional	Everolimus: 2% Placebo: 1%	mPFS: Everolimus: 11.0 mo Placebo: 3.9 mo	HR: 0.64;95% CI: 0.40, 1.05; p= 0.037
Ph II Carcinoids and pNET study (n=109) (Kulke 2008)	Sunitinib (2L, prior chemo allowed)	Carcinoid (n=41) pNET (n=66)	Carcinoid: 2.4% pNET: 16.7%	mTTP**: carcinoid:10.2 mo pNET: 7.7 mo	1-yr OS rate Carcinoid: 83.4%; pNET:81.1%
Ph III pNET study (n=171) (Raymond 2011)	Sunitinib vs. Placebo (1:1)	G1/2 advanced pNET	Sunitinib: 9.3% Placebo: 0%	mPFS: Sunitinib:11.4 mo Placebo: 5.5 mo HR: 0.42 (p=0.001	HR: 0.41 p=0.02
Ph III RADIANT-3 pNET study (n=410) (Yao 2011)	Everolimus vs. Placebo (pretreated SSA, Chemo)	Advanced, low or intermediate grade pNET	Everolimus: 4.8% Placebo 2.0%	mPFS: Everolimus: 11 mo Placebo: 4.6 mo	NR
Phase III NETTER-1 Midgut NET (n= 299) (Strosberg 2016)	PRRT + OCT vs. OCT	Advanced, well-differentiated Midgut	PRRT: 1.8% OCT: 3%	mPFS: PRRT: Not reached OCT: 8.4 mo HR: 0.209	NR
*NR = Not reported ** mTTP = median Time To Progression					

The treatment strategies of poorly-differentiated neuroendocrine carcinoma are often extrapolated from the treatment paradigm of small cell lung cancer (SCLC) (Sorbye 2014). There are no prospective studies conducted in gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC), most of the studies reported are retrospective with limited sample size. Based on its established role in SCLC, cisplatin and etoposide is the most widely used regimen in GEP-NET in the front line setting with response rates in the range of 42% to 67% and median survival of approximately 15 to 19 months (Moertel 1991; Mirty 1999). More recent data suggest that the clinical outcome in patients with GEP-NEC may be worse than previously reported. In a retrospective study, 252 patients with advanced GEP-NEC received cisplatin/etoposide or carboplatin/ etoposide (Sorbye 2013) reporting an ORR of 31%, median PFS of 4 months with a median survival of 11 months. No differences in outcome were observed when comparing cisplatin-based treatment versus carboplatin-based treatment. Upon progression on front line platinum based therapy, no standard therapy has been established for GEP-NEC. Retreatment with cisplatin is an option as well as different regimens are considered (including FOLFOX, XELOX, temozolamide plus capecitabine) as well as single agent therapy (including temozolamide, irinotecan, taxanes or amrubicin) (Garcia-Carbonero 2016). On small retrospective studies, the response rates ranges from 18% to 31%; with a median PFS of approximately 4 months and survival in the range of 6 to 9 months (Hadoux 2013; Hentic 2012; Olsen 2012).

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

1.2.1 Overview of PDR001

PDR001 is a high-affinity, ligand-blocking, humanized IgG4 antibody directed against Programmed Death-1 (PD-1) receptor that blocks the binding of PD-L1 and PD-L2. PD-1 is a critical immune-checkpoint receptor that is expressed on CD4 and CD8 T cells upon activation (Freeman 2008). Engagement of PD-1 by its ligands, PD-L1 and PD-L2, transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function (Riley 2009). Monoclonal antibody (mAb) inhibitors of immunological checkpoints, including PD-1 and PD-L1, have demonstrated significant antitumor activity in patients with various solid tumors. For further details please refer to the latest PDR0001 [Investigator's Brochure].

1.2.1.1 Non-clinical experience of PDR001

PDR001 binds specifically and with high affinity to human PD-1 and enhances interleukin-2 production in *ex-vivo* lymphocyte stimulation assays. It does not cross react with rodent PD-1; therefore, toxicology studies were performed only in cynomolgus monkeys where there was acceptable cross reactivity with monkey PD-1. Repeat administration of PDR001 to monkeys was tolerated at all doses tested up to 100 mg/kg/week for 5 weeks in the GLP toxicology single-agent study. No test article-related in-life, mortality, organ weight changes, or macroscopic findings were noted. There were no PDR001-related effects seen in any of the safety pharmacology endpoints assessed (cardiovascular, neurobehavioral, and respiratory). Macrophage infiltrates into the splenic white pulp were observed in animals given 100 mg/kg/week and mononuclear cell infiltrates, often associated with fibrosis, around the injection site blood vessel (saphenous vein) in a few animals given ≥25 mg/kg/week. These PDR001-related microscopic changes were fully reversible after an eight week recovery. Additionally, mostly low grade mononuclear infiltrates in the vascular and perivascular space in several tissues of main and recovery treated animals and in recovery controls were observed but with a slightly higher incidence in treated animals. No evidence of parenchymal damage was associated with the vascular/perivascular changes in any of the organs examined and the changes were not associated with any frank tissue injury. Dose-proportional exposure to PDR001 in each dose group was confirmed. Anti-drug antibodies (ADA) to PDR001 were observed in some PDR001 treated cynomolgus monkeys. A trend of reduced drug exposure was observed in these ADA-positive animals. Based on the toxicology studies with PDR001 as a single-agent, the Highest Non-Severely Toxic Dose (HNSTD) dose is 100 mg/kg. For further details, please refer to the latest PDR001 [Investigator's Brochure].

1.2.1.2 Clinical experience of PDR001

At the time of the release of the protocol amendment 2; three studies assessing PDR001 single agent in patients with advanced solid tumors as well as other malignancies (including melanoma, non-small cell lung cancer, triple negative breast cancer and anaplastic thyroid cancer) have reported preliminary safety data included in the Investigator Brochure version 6.

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CPDR001X2101 Study:

A summary of preliminary clinical safety information reported from the first-in-human study is provided below (cut-off date 14-Nov-2016):

A total of 160 patients were exposed to PDR001 single-agent. In the phase I part of the study, 58 patients had been treated at doses of 1 mg/kg Q2W (16 patients) for up to 78 weeks, 3 mg/kg Q2W (15 patients) for up to 60 weeks, 10 mg/kg Q2W (11 patients) for up to 34 weeks, 3 mg/kg Q4W (6 patients) for up to 33 weeks and 5 mg/kg Q4W (10 patients) for up to 57 weeks. In the phase II part of the study, 102 patients had been treated in five groups: NSCLC 400 mg Q4W (33 patients), NSCLC 300 mg Q3W (1 patient), melanoma 400 mg Q4W (24 patients), TNBC 400 mg Q4W (40 patients) and anaplastic thyroid cancer 400 mg Q4W (4 patients). In the phase II part of the study, the median duration of exposure to study treatment was 8.0 weeks (range 1.0 - 35.1). No Dose Limiting Toxicities (DLTs) were reported. One-hundred twenty seven patients (79.4 %) have permanently discontinued study treatment, 5 due to an AE, 97 due to progression of disease, 8 due to subject/guardian decision, 4 due to physician decision and 13 due to death. None of the deaths were attributed to study treatment.

Of the 160 patients treated, 79 (49.4 %) experienced AEs (all grades) suspected to be related to study treatment. Most frequent suspected AEs (≥ 5 % of patients) included fatigue (24 patients, 15.0 %), nausea (14 patients, 8.8 %), pruritus (13 patients, 8.1 %), diarrhea (12 patients, 7.5 %) and hypothyroidism (10 patients, 6.3 %). Of the 160 patients treated, 84 (52.5 %) experienced grades 3 or 4 AEs regardless of relationship to study drug. Of these grades 3/4 AEs, the following were suspected to be related to study treatment: two cases of vomiting and individual cases of increased ALT, increased AST, hypocalcemia, increased lipase, autoimmune hepatitis, autoimmune colitis, nausea, hyperglycemia, decreased lymphocyte count, and decreased weight. SAEs regardless of relationship to study drug, were reported in 61 (38.1 %) patients. Seven serious adverse events (SAEs) were observed in five patients were suspected to be related to study treatment per investigator's assessment.

CPDR001X1101 Study:

A summary of preliminary clinical safety information reported from this study conducted in Japanese patients with solid tumors is provided below (cut-off date 25-Nov-2016):

Eighteen patients had been enrolled and treated with PDR001 at doses of1 mg/kg Q2W (6 patients) for up to 27 weeks, 3 mg/kg Q2W (6 patients) for up 28 weeks, and 10 mg/kg Q2W (6 patients) for up to 14 weeks. No DLTs were reported. Sixteen patients (88.9 %) have permanently discontinued study treatment, 2 patients (11.1 %) due to an AE, 6 patients (33.3 %) due to progression of disease, and 8 patients (44.4 %) due to physician or subject/guardian decision. AEs suspected to be related to study treatment: Of the 18 patients treated, 11 patients (61.1 %) experienced AEs (all grades) suspected to be related to study treatment. The most frequent suspected (≥ 10 % of patients) AEs included maculo-papular rash (4 patients, 22.2 %), ALP increased (2 patients, 11.1 %) and malaise (2 patients, 11.1 %). Of the 18 patients treated, nine patients (50.0 %) experienced grade 3 or grade 4 AEs regardless of relationship to study drug. Of note, one grade 3 ALT increased and one grade 3 creatine phosphokinase increased were suspected to be related to study treatment. SAEs, all grades, regardless of relationship to study drug, were reported in 7 (38.9 %) patients. Two SAEs (grade 2 myositis and grade 1

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interstitial pneumonia) were suspected to be related to study treatment per investigator's assessment.

CPDR001X2201 Study:

A summary of preliminary clinical safety information reported from this study conducted in patients with nasopharyngeal carcinoma is provided below (cut-off date: 02-Dec-2016):

Thirty-two patients had been enrolled and treated with PDR001 at the dose of 400 mg Q4W for up to 23 weeks. Fourteen patients (43.8 %) have permanently discontinued study treatment, 11 (34.4 %) due to progression of disease, 1 (3.1 %) due to physician decision, 1 (3.1 %) due to subject/guardian decision and 1 (3.1 %) due to death (caused by progressive disease). Eighteen (56.3 %) patients are still on treatment. Of the 32 patients treated, 16 (50%) experienced AEs (all grades) suspected to be related to study treatment. The most frequent suspected AEs included fatigue, pyrexia, rash and hyponatremia (each in 3 patients, 9.4%), pneumonia, asthenia, decreased appetite and malaise were observed in 2 patients (6.3%). Of the 32 patients, 11 (34.4 %) experienced grade 3 or grade 4 AEs regardless of relationship to study drug. Grade 3 or 4 AEs suspected to be related to PDR001 were observed in 5 (15.6 %) patients. These included 3 patients with hyponatremia (9.4 %), 2 patients with pneumonia (6.3 %) and 1 patient with decreased appetite (3.1 %). SAEs, all grades, regardless of relationship to study drug, were reported in 7 (21.9 %) patients treated with PDR001. Three patients experienced an SAE suspected to be related to study drug.

For additional details on the monotherapy studies above mentioned or on ongoing studies with PDR001 in combination with other agents, please refer to the PDR001 Investigator Brochure.

CPDR001E2201 Study: Results of the interim and additional efficacy analysis

Planned interim analysis was performed with a data cut-off of 29-Nov-2017 after approximately 30 patients in the well-differentiated NET group had undergone the first 3 radiological assessments, had shown disease progression, or had discontinued efficacy follow-up for any other reason. The full analysis set included 95 patients in the well-differentiated NET group (30 patients in the thoracic cohort, 33 patients in the pancreatic cohort and 32 patients in the GI cohort) and 21 patients in the poorly-differentiated GEP-NEC group. Median duration (range) of follow-up (from treatment to data cut-off date) was 5.3 months (3.7-8.5 months) and 3.6 months (2.3-4.6 months) in the well-differentiated NET and poorly-differentiated GEP-NEC groups, respectively. With this limited follow up, the overall response rate (ORR) per RECIST 1.1 based on central radiology review was 3.2% in the well-differentiated NET group (10.0 % in the thoracic cohort, 0% in the pancreatic cohort, and 0% in the GI cohort) and 0% in the poorly-differentiated GEP-NEC group.

Safety analysis excluded events occuring 30 days after study treatment discontinuation. The most common adverse events (AEs) (≥15% in all patients; all grades) reported at the time of the interim analysis were fatigue (34.7% in well-differentiated NET cohort and 14.3% in poorly-differentiated GEP-NEC cohort), pyrexia (25.3% and 9.5%, respectively), diarrhea (20.0% and 14.3%, respectively), nausea (16.8% and 28.6%, respectively), abdominal pain (18.9% and 9.5%, respectively), and constipation (16.8% and 14.3%, respectively). The most common grade 3/4 AEs (≥2 of patients in each group) in well-differentiated NET cohort were abdominal pain and anemia (each in 4 patients), hypertension (3 patients), and fatigue and dyspnoea (each

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in 2 patients). Abdominal pain, cough and back pain (each in 2 patients) were the most common grade 3/4 AEs in poorly-differentiated GEP-NEC cohort. No fatal SAEs were reported at the time of this analysis.

An additional efficacy analysis was performed with a data cut-off of 09-Feb-2017. The ORR per RECIST 1.1 based on central radiology review, was 7.4% (7 patients with partial response [PR]) in the well-differentiated NET group and 4.8% (1 patient with PR) in the poorly-differentiated GEP-NEC group. In the well-differentiated NET group, the ORR in 3 different cohorts were: 20.0% in the thoracic cohort (6 patients with PR of 30 evaluated; assessments of response duration was limited by the 2 deaths observed among 6 responders), 3.0% in the pancreatic cohort (1 patient with PR of 33 evaluated), and 0 in the GI cohort (of 32 evaluated; however, 1 unconfirmed PR was reported in the GI cohort at the time of the cut-off).

The study is ongoing and further assessments for efficacy and safety continue. The primary analysis of the study will be performed 1 year after Last Patient First Treatment (LPFT) in the initially enrolled well-differentiated NET group.

2 Rationale

2.1 Study rationale and purpose

During tumorigenesis, cancer cells from a wide range of tumor types exploit immune checkpoint pathways, such as PD-1, 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 to improved cytolytic activity towards tumors. Additionally, PD-1 blockade is associated with a reduced numbers of regulatory T cells (Tregs) at the tumor site (Wang 2009, Mangsbo 2010).

Monoclonal antibody (mAb) inhibitors of immunological checkpoints, including anti-PD-1 and anti-PD-L1, have demonstrated significant antitumor activity in patients with various solid tumors. Two mAbs targeting PD-1, pembrolizumab and nivolumab, have demonstrated significant single agent activity in melanoma, non-small cell lung cancer, renal cancer, head neck cancer and Hodgkin's lymphoma among other solid tumors (Topalian 2012, Hamid 2013b, Topalian 2014, Seiwert 2014, Motzer 2015, Gillison 2016; Ansell 2015).

Although many advances with checkpoint inhibitors have been made in other tumor types, the data generated in NETs is limited with no clinical experience available to date. Recent correlative studies conducted in NETs have assessed the expression of PD-L1 and correlated tumor differentiation with poor clinical outcome (Kim 2016; Cives 2016).

Tumor-infiltrating lymphocytes (TILs) have been shown to predict survival in numerous malignancies. The importance of TILs in PNET and NET with liver metastases was assessed by immunohistochemistry (IHC) in a cohort of 126 patients who had undergone resection. Analysis of intermediate-grade NETs indicated that a dense T cell (CD3+) infiltrate was associated with a median relapse-free-survival (RFS) of 128 months compared with 61 months for those with low levels of intratumoral T cells infiltrate ($P = 0.05$, univariate analysis). Examination of liver metastasis revealed that a low level of infiltrating regulatory T cells (Treg, FoxP3+) was a predictor of prolonged survival ($P < 0.01$, univariate analysis). Therefore a

[redacted]

robust T cell infiltration is associated with improved RFS following resection of intermediate-grade NETs, whereas the presence of a tumor environment rich in Tregs correlated with shorter OS after treatment (Katz 2010). These findings suggest that the immune-modulation of the phenotype of T cells may play a role in clinical outcome.

PD-L1 and PD-1 expression was assessed by immunohistochemical analysis in tumor samples of 80 patients with lung NET showing a 59% and 51.3% expression rate, respectively (Fan 2016). A similar analysis was conducted on 20 corresponding cancer-adjacent tissue specimens revealing an expression rate of 25% and 20% for PD-L1 and PD-1, respectively. PD-L1 expression was significantly related to tumor stage and histological type (carcinoids, SCLC, LCNEC) (p=0.014). Survival analysis demonstrated a correlation with PD-L1 expression in tumor cells (8.9 months in PD-L1 Positive vs. 25.6 months in PD-L1 Negative); this correlation was also observed in tumor in TILs (8.9 months in PD-L1 Positive vs. 26.8 months in PD-L1 Negative). This results suggest that PD-L1 expression can be useful prognostic marker for survival.

PD-L1 expression on tumor cells was analyzed by immunohistochemistry in 32 patients with GEP-NET showing a 22% expression rate in tumors (Kim 2016). PD-L1 expression was significantly associated with high-grade tumors (p=0.008). Moreover, the status of PD-L1 expression could predict survival; the median overall survival (mOS) was 16.0 months in patients with PD-L1–positive tumors and 24.8 months in those with PD-L1 negative tumors (p=0.037).

Clinical data available from one patient with histologically confirmed metastatic atypical pulmonary carcinoid treated in the ongoing PDR001 phase I study in solid advanced tumors [CPDR001X2101] showed an immune-related partial response with resolution of multiple liver and pleural metastases. The patient is a non-smoker, and tumor histology has been confirmed by central pathology as consistent with atypical carcinoid. Interestingly, tumor from this patient harbored 19 non-synonymous mutations only on the whole exome sequencing, suggesting that mutational burden in carcinoid tumors may not be the main driver of response to immune checkpoint inhibitors therapy. Patient has been on therapy for nine months, and at the last tumor imaging assessment a sustained partial response according to RECIST 1.1 criteria was observed with sustained regression in all areas of tumor (Naing 2016).

2.2 Rationale for the study design

A single arm study with a primary endpoint of overall response rate (ORR) with supportive key secondary endpoint of duration of response (DoR) is proposed to assess the safety and efficacy of PDR001 in two different groups of patients:

- Patients with well-differentiated (G1 or G2) non-functional, unresectable advanced or metastatic NETs of GI, pancreatic or thoracic origin who have progressed on or after prior available treatments.
- Patients with advanced or metastatic poorly-differentiated GEP-NEC who have progressed on or after one prior chemotherapy regimen.

A total of approximately 90 patients will be enrolled in the well-differentiated group, with approximately 30 patients enrolled in each cohort based on tumor origin. Approximately 20 patients will be enrolled in the poorly-differentiated GEP-NEC group.

[redacted]

For patients with well-differentiated non-functional NET who present with disease progression after treatment with prior therapy (SSAs, cytotoxic agents and/or targeted therapies depending on the anatomical tumor site), there are currently no approved therapies improving the clinical outcome (Section 1.1). For patients with poorly-differentiated GEP-NEC no treatments are currently approved and currently there is no consensus with regards to the standard of care upon progression on first line treatment which typically consists of chemotherapy.

In the absence of an established treatment to be considered as control, and based on the fact that ORR endpoint is appropriate to detect early signs of efficacy in the absence of a control (see below), a single arm study design has been proposed.

A single arm design with an endpoint of ORR with DoR as a key secondary endpoint has been utilized as a primary means of evaluation in disease settings where an appropriate comparator may not necessarily exist or where currently available therapy does not provide sufficient evidence of benefit. Specifically in patients with well-differentiated NET, a considerably long overall survival and heterogeneity of survival prognostic factors make a survival endpoint unsuitable for an early read-out of treatment efficacy for a novel agent (Yao 2008). The study design as proposed is expected to provide initial evidence of benefit by showing an improvement in ORR, supported by duration of response, which based on clinical experience with PD-1 inhibitors, should serve as an appropriate surrogate to predict clinical benefit. A uniformly low ORR has been reported in well-differentiated NET from all tumor origins in patients receiving placebo or best supportive care in randomized studies (ranging from 0% to 2%), (Table 1-1). In patients with advanced and progressive NETs, where available treatments have failed, an improvement in terms of ORR would be a relevant indicator of treatment efficacy.

With regards to poorly-differentiated GEP-NEC, there are limited published results, mostly from retrospective studies reporting on small series of patients with advanced /metastatic disease. For this reason, the analysis of the data from this group of patients intends to explore the antitumor activity of PDR001 in this population with a high unmet medical need.

2.3 Rationale for dose and regimen selection

In study [CPDR001X2101], PDR001 single-agent was administered as an intravenous infusion over 30 minutes at doses ranging from 1 to 10 mg/kg on an every 2 weeks (Q2W) schedule or at 3 and 5 mg/kg every 4 weeks (Q4W) schedules. Approximately dose-proportional increase in exposure (C1D1 AUC0-336) was observed with doses from 1 to 10 mg/kg and no DLTs were observed. Accumulation of approximately 2.1-3.4-fold was observed with Q2W dosing and 1.6-2.2-fold with Q4W dosing. Population PK analysis indicated that the changes in exposure due to patient weight differences are minimal across the anticipated weight range of 30 to 150 kg for the patient population. Therefore, a flat dosing scheme was selected. Two recommended phase II dosing regimens have been established: 300 mg Q3W and 400 mg Q4W flat dosing schedules. A flat dose of 400 mg Q4W or 300 mg Q3W is expected to achieve a mean steady-state Ctrough value higher than the ex vivo EC50 for antigen-stimulated IL-2 production, a translational biomarker for PD-1 blockade (Patnaik et al, 2015). Based on the safety profile observed in study [CPDR001X2101] (Section 1.2) and the expected Ctrough values, 400 mg Q4W is expected to be a safe and efficacious dose.

[redacted]

2.4 Rationale for choice of comparators drugs

Not applicable

2.5 Risks and benefits

PDR001 is a humanized IgG4 monoclonal antibody which belongs to a class of agents known as immune-checkpoint inhibitors specifically anti-PD-1/PD-L1. This class of compounds has demonstrated significant improvement in efficacy combined with a tolerable and manageable safety profile, thus supporting recent regulatory approvals in melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck, bladder cancer, renal cancer and Hodgkin's lymphoma.

Immune-checkpoint inhibitors including anti-PD-1/PD-L1 may be associated with the occurrence of immune-mediated adverse events (irAE). In general, irAE can potentially involve every organ system but gastrointestinal (colitis), dermatologic, hepatic (hepatitis), pulmonary (pneumonitis), renal (nephritis) and endocrine toxicities (hypothyroidism, hyperthyroidism, diabetes, hypophysitis and hypopituitarism) are the most frequent and rarely CNS (encephalitis). These side effects are generally manageable but fatal events have been reported in some cases with checkpoint inhibitor compounds (Eggermont 2015; Larkin 2016; Hofmann 2016).

Appropriate eligibility criteria as well as specific dose modification and stopping rules along with AE management guidelines (provided in Section 6.3.1), are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events i.e., skin toxicity and diarrhea are provided in Section 6.3.1.2. The risks to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures as well as, close clinical monitoring. There may be unforeseen risks with PDR001 which could be serious. Refer to preclinical toxicity and or clinical data found in the latest [Investigator's Brochure].

For patients with unresectable locally advanced or metastatic non-functioning NETs progressing on or after currently available therapies, available treatment options are limited (Section 1.1). For this reason, PDR001 treatment may provide clinical benefit which will be measured as tumor shrinkage (ORR) and time-related parameters (including duration of response, PFS, and OS rates at 1 and 2 years).

The efficacy endpoints will be assessed as per RECIST 1.1 (Appendix 1). Patients may continue treatment beyond disease progression by RECIST 1.1 and until disease progression by irRECIST if the criteria stipulated in Section 6.1.5.1 are met. This measure intends to minimize the risk of early treatment discontinuation for patients who are receiving immune- based treatment and experiencing clinical benefit and to allow enough time for the patient's immune system to elicit an effective antitumor response, if it were to develop.

Taking into consideration the safety profile observed so far, the unmet medical need in this population of patients with NET after treatment failure with available standard therapy and the measures implemented in the protocol to minimize the risks described above, the benefit-risk assessment is deemed acceptable to conduct this study in patients with NETs as part of the global clinical development of PDR001.

[redacted]

3 Objectives and endpoints

Objectives and related endpoints are described in the table below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint(s)	Analysis
Primary		Refer to Section 10.4
To estimate the antitumor activity of PDR001 as a single agent in the well-differentiated NET and poorly-differentiated GEP-NEC groups.	ORR (confirmed PR and CR) according to blinded independent review committee (BIRC) radiological assessment by RECIST 1.1	
Key secondary		Refer to Section 10.5.1
To estimate efficacy of PDR001 in the well-differentiated NET and poorly-differentiated GEP-NEC groups	Duration of Response (DoR) by RECIST 1.1 and as per BIRC	
Other secondary		Refer to Section 10.5.2
To assess the safety and tolerability of PDR001 in each group and in the overall study population	Frequency and severity of adverse events Other safety data as considered appropriate	Refer to Section 10.5.3
To evaluate additional efficacy parameters in the well-differentiated NET and poorly-differentiated GEP-NEC groups	Disease Control Rate (DCR), Time to Response (TTR), PFS by RECIST 1.1 and as per BIRC Immune Response Criteria by irRECIST and as per BIRC (irORR, irDoR, irTTR, irDCR, irPFS) 1-year and 2-year overall survival (OS) rate	Refer to Section 10.5.2
To evaluate biochemical response to treatment (based on CgA and NSE) in the well-differentiated NET and poorly-differentiated GEP-NEC groups	Changes from baseline in CgA and NSE	Refer to Section 10.5.6
To characterize the pharmacokinetics of PDR001 with 400 mg flat dose Q4W in the well-differentiated NET and poorly-differentiated GEP-NEC groups	PK parameters (e.g. Ctrough)	Refer to Section 10.5.4
To characterize patient's health-related quality of life with PDR001 in the well-differentiated NET and poorly-differentiated GEP-NEC groups	Global health status/QOL score of the EORTC QLQ-C30 and the index score of the EQ-5D-5L	Refer to Section 10.5.8
To evaluate the prevalence and incidence of immunogenicity in the well-differentiated NET and poorly-differentiated GEP-NEC groups	Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment	Refer to Section 10.5.5

[redacted]

[redacted]

[redacted]

4 Study design

4.1 Description of study design

This is a phase II, single-arm, open-label, multi-center study in patients with

- Well-differentiated, non-functional, grade 1 or 2, neuroendocrine tumors of pancreatic, GI or thoracic (including lung and thymus) origins and
- Poorly-differentiated GEP-NEC

All patients must have progressed on or after the last treatment. (as described in Section 5.1).

A total of approximately 90 patients will be enrolled in the well-differentiated group, with approximately 30 patients enrolled in each cohort based on tumor origin. Approximately 20 patients will be enrolled in the poorly-differentiated GEP-NEC group, for a total number of approximately 110 patients.

Treatment duration

Patients will receive PDR001 at the dose of 400 mg Q4 weeks at flat dosing. Patients will continue to receive the assigned study treatment until disease progression by RECIST 1.1 or as per irRECIST (see below), unacceptable toxicity, start of a new anti-neoplastic therapy, withdrawal of consent, physician's decision, lost to follow-up, death or the study is terminated by the sponsor.

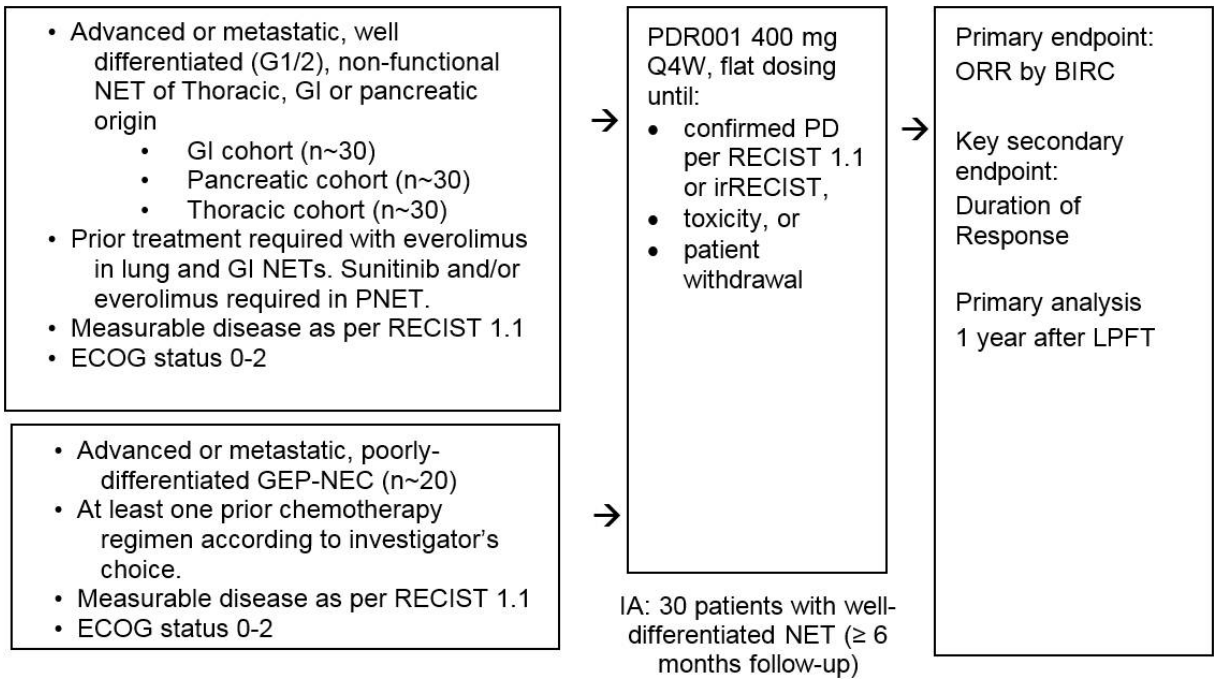
Patients may continue study treatment beyond disease progression by RECIST 1.1 until disease progression as per irRECIST, as per BIRC (if criteria stipulated in Section 6.1.5.1 are fulfilled), unacceptable toxicity, start of new anti-neoplastic therapy, withdrawal of consent, physician's decision, lost to follow-up, death, or the study is terminated by the sponsor. In case of continuation of study treatment beyond disease progression by RECIST 1.1, the patient will continue assessments as defined in Section 7. While the investigator is waiting for the results from the central imaging vendor confirming disease progression, the patient should continue on study treatment. However, during this time, the investigator should do whatever is medically necessary for his/her patient.

[redacted]

After the primary analysis cut-off date (10-Aug-2018):

- Response assessments by BIRC will no longer be performed.
- Patients, who are on treatment but have not yet progressed per local tumor response assessment, will continue study treatment until documentation of disease progression by RECIST 1.1 as per local investigator assessment, unacceptable toxicity, start of new anti-neoplastic therapy, withdrawal of consent, physician's decision, subject/guardian decision, lost to follow-up, death or the study is terminated by the sponsor. These patients will be permitted to continue study treatment beyond initial PD as per RECIST 1.1 until confirmed irPD per local assessment (until 2 consecutive irPDs), as described in Section 6.1.5.1.
- Patients who are on treatment beyond disease progression per local tumor response assessment (tumor assessment performed before the primary analysis cut-off date (10-Aug-2018)) are allowed to continue study treatment as long as the patient derives clinical benefit from the treatment according to investigator's best clinical judgement (e.g. no deterioration of performance status, no rapid increase in tumor burden, no clinical situation requiring alternative treatment), or until unacceptable toxicity, start of new anti-neoplastic therapy, withdrawal of consent, lost to follow-up, death, or the study is terminated by the sponsor.

Figure 4-1 Study design



4.1.1 Study flow

The study is comprised of the following periods:

- Screening
- Treatment

[redacted]

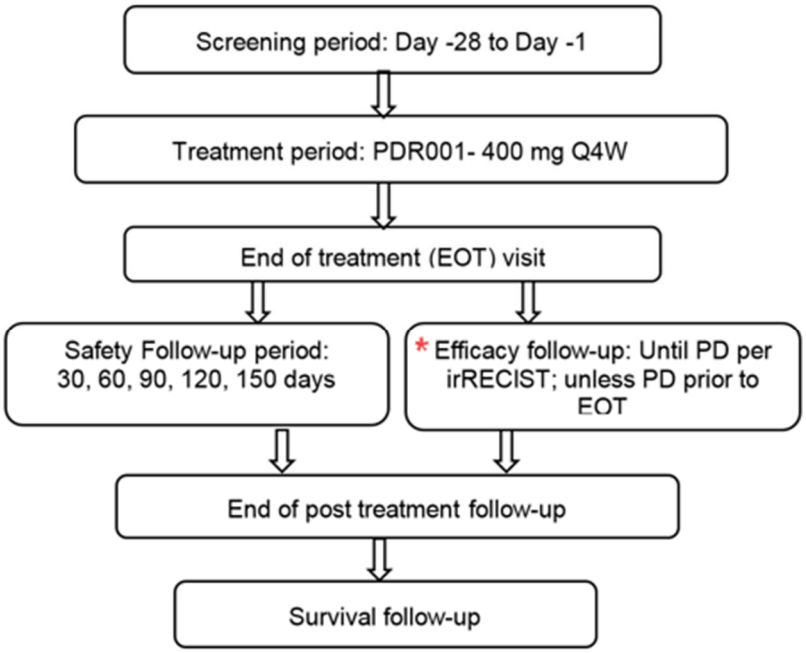
- End of Treatment (EOT)
- Safety follow-up: patients will be followed for safety at 30-Days, 60-Days, 90-Days, 120-Days, and 150-Days after the last dose of PDR001 (Section 7.1.7)
- Post-treatment efficacy follow-up:
  - Before the primary analysis cut-off date (10-Aug-2018), patients who discontinue treatment for reasons other than irRECIST PD will have tumor assessments per Table 7-1 until withdrawal of consent, death, lost to follow-up, or eventual irRECIST PD per BIRC even if new antineoplastic treatment (ANP) is started (Sections 7.1.8 and Section 7.2.1)
  - After the primary analysis cut-off date (10-Aug-2018), post-treatment efficacy follow-up will be discontinued. Therefore, any patients, who are in post-treatment efficacy follow-up at the time of the primary analysis cut-off date, will enter the survival follow-up after completion of the safety follow-up. If clinically indicated, patients may continue to undergo tumor response assessments during the safety follow-up according to local or institutional standard of care; however these tumor response assessments will no longer be reported in the eCRF.
- Survival follow-up: patients will be followed for survival every 3 months after the completion of safety or efficacy follow-up, whichever is last

For a diagram of the study flow, see Figure 4-2. Patients will undergo safety and efficacy assessments during screening, treatment, and follow-up as outlined in Table 7-1 visit evaluation schedule.

This study will use third-party vendors for central imaging, central laboratory, ePRO (e.g., electronic tablet devices to collect patient-reported outcomes (PRO) data), and eligibility checklist plus drug supply management via Interactive Response Technology (IRT). After the primary analysis cut-off date (10-Aug-2018) ePRO and central tumor response assessments will no longer be performed and/or collected.

[redacted]

Figure 4-2 Study flow



*After the the primary analysis cut-off date (10-Aug-2018), post-treatment efficacy follow-up will no longer be performed.

4.2 Timing of interim analysis and design adaptations

A planned interim analysis (IA) will be conducted after approximately 30 patients in the well-differentiated NET group have undergone the first 3 radiological assessments (expected around week 24) or have shown disease progression or have discontinued efficacy follow-up for any other reason. All available efficacy and safety data from well-differentiated NET and poorly differentiated GEP-NEC groups up to the cut-off date will be used for the IA and reviewed by the Steering Committee (see Section 10.7 for more details). It is expected that at the time of the interim analysis all patients from the poorly-differentiated GEP-NEC group have undergone at least 2 radiological assessments. The study will not be stopped at the interim analysis for efficacy reasons regardless of results and will be continued until mature data from all patients become available.

4.3 Definition of end of study

Cut-off date for the primary analysis will be 1 year after Last Patient First Treatment (LPFT) in the initially enrolled well-differentiated NET group. This analysis will include data from patients with well-differentiated NET and poorly-differentiated GEP-NEC groups who were enrolled in the study. It is expected that at the time of this analysis all patients from the original poorly-differentiated GEP-NEC group will have at least 11 months follow-up. This analysis will be summarized in the clinical study report (CSR).

If the analysis results are not conclusive or do not meet the pre-specified study criteria (refer to Section 10.4), the treatment continuation for patients who are benefitting from PDR001

treatment will be assessed on a case-by-case basis in consultation with the sponsor. Patients who discontinue study treatment will complete the safety follow-up period.

The end of study is defined as the earliest occurrence of one of the following :

- All patients have discontinued treatment and completed safety follow-up period.
- If another clinical study becomes available that can continue to provide treatment with PDR001 in this patient population and all ongoing patients are eligible to be transferred to that clinical study (and do not meet any discontinuation criteria from study CPDR001E2201).
- At the end of the study, every effort will be made to continue provision of investigational treatment outside this study through an alternative setting to patients who in the opinion of the Investigator are still deriving clinical benefit.

4.4 Early study termination

If the study is stopped for safety reasons, recruitment will be terminated, and the treatment continuation of patients who are deriving benefit from PDR001 treatment will be assessed on a case-by-case basis in consultation with the sponsor.

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.6 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The study will include two groups of adult patients with advanced (unresectable or metastatic):

- Well-differentiated (G1/2), non-functional, neuroendocrine tumor of GI, pancreatic or thoracic (lung/thymus) origin who have progressed on prior treatment
- Poorly-differentiated GEP-NEC who have progressed on or after one prior chemotherapy regimen.

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 met.

5.2 Inclusion criteria

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

1. Written informed consent must be obtained prior to any screening procedures
2. Adult males or females ≥ 18 years at screening.
3. Pathologically confirmed, advanced (unresectable or metastatic):

[redacted]

- Well-differentiated (G1 /2) based on local pathology report, non-functional neuroendocrine tumor of GI, pancreatic or thoracic (including lung and thymus) origin.
- Poorly-differentiated GEP-NEC based on local pathology report

4. No active symptoms related to carcinoid syndrome during the last 3 months prior to start of study treatment.
5. Patients must have received prior treatment for advanced disease:
   - Well-differentiated NET group:
   a. Thoracic (lung and thymus origin) cohort:
      - Thymus origin: at least one prior systemic therapy according to investigator's choice
      - Lung origin: at least one prior systemic therapy is required, which must include everolimus.
   b. GI cohort: at least two prior systemic regimens, which must include everolimus. Prior systemic therapies may include: somatostatin analogs, PRRT, and/or chemotherapy.
   c. pNET cohort: at least two prior systemic regimens, which must include everolimus and/or sunitinib. Prior systemic therapies may include: somatostatin analogs, PRRT and/or chemotherapy.

   Note: For well-differentiated NET, prior treatment with interferon alpha is allowed provided that it is not the last treatment received prior to study entry.
   - Poorly-differentiated GEP-NEC group: at least one prior chemotherapy regimen according to Investigator's choice.
6. Radiological documentation of disease progression :
   - Well-differentiated NET group: Disease progression while on/or after the last treatment, and this progression must have been observed within 6 months prior to start of study treatment (i.e. maximum of 24 weeks from documentation of progression until study entry). Disease must show evidence of radiological disease progression based on scans performed not more than 12 months apart.
   - Poorly-differentiated GEP-NEC group: Disease progression while on or after prior treatment.
7. At least one measurable lesion assessed by CT and/or MRI according to RECIST 1.1.
   Note: Any lesions which have been subjected to percutaneous therapies or radiotherapy should not be considered measurable, unless the lesion has clearly progressed since the procedure.
8. Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
9. Tumor biopsy material must be provided for all patients [redacted]:
   - Well-differentiated (G1/2) NET: Biopsy material must be provided following the diagnosis of metastatic disease. The tumor sample must be collected from a metastatic site not previously irradiated and **should preferably be taken within 6 months but not more than 24 months prior to start of study treatment.**

[redacted]

- Poorly-differentiated GEP-NEC: Biopsy material must be collected from the primary tumor or from a metastatic site not previously irradiated, **taken not more than 24 months prior to start of study treatment.**

10. Women of childbearing potential must have had a negative serum pregnancy test within 72 hours prior to the start of study treatment. Highly effective contraception must be used while on study.
11. Patient is deemed by the investigator to have the ability and means to be compliant with the protocol (treatment and follow-up).
12. Patient must meet the following laboratory values at the screening visit:
    - Absolute Neutrophil Count $\geq 1.5 \times 10^9$/L
    - Platelets $\geq 75 \times 10^9$/L
    - Hemoglobin (Hgb) ≥9 g/dL
    - Serum creatinine <1.5 mg/dL
    - Total bilirubin ≤1.5 x ULN
    - Aspartate transaminase (AST) ≤ 3.0 x ULN, except for patients with liver metastasis, if AST ≤5.0 x ULN
    - Alanine transaminase (ALT) ≤ 3.0 x ULN, except for patients with liver metastasis, if ALT ≤5.0 x ULN

5.3 Exclusion criteria

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

1. Well-differentiated, grade 3 neuroendocrine tumors; poorly-differentiated neuroendocrine carcinoma of any origin (other than GEP-NEC); including NEC of unknown origin, adenocarcinoid, and goblet cell carcinoid.
2. Pretreatment with interferon as last treatment prior to start of study treatment
3. Prior treatment for study indication with:
    a. Antibodies or immunotherapy within 6 weeks before the first dose of study treatment.
    b. PRRT administered within 6 months of the first dose.
    c. Systemic antineoplastic therapy (including cytotoxic chemotherapy, and toxin immune conjugates) or any experimental therapy within 14 days or 5 half-lives, whichever is longer, before the first dose of study treatment. For cytotoxic agents that have major delayed toxicities a washout period of more than 6 weeks is indicated (examples are nitrosoureas and mitomycin C).
    d. Tyrosine kinase inhibitors within 14 days or 5 half-lives, whichever is longer, before the first dose of study treatment.
    e. Prior PD-1- or PD-L1-directed therapy.
    f. Cryoablation, radiofrequency ablation, or trans-arterial embolization of hepatic metastases within 2 months before the first dose of study treatment.
4. Systemic chronic steroid therapy (≥ 10mg/day prednisone or equivalent) or any immunosuppressive therapy 7 days prior to planned date for first dose of study treatment. Topical, inhaled, nasal and ophthalmic steroids are allowed.

[redacted]

5. Any untreated central nervous system (CNS) lesion. However, patients are eligible if: a) all known CNS lesions have been treated with radiotherapy or surgery and b) patients remained without evidence of CNS disease progression ≥ 4 weeks after treatment and c) patients must have discontinued corticosteroid therapy for ≥ 2 weeks.
7. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma in situ.
8. Major surgery, open biopsy, or significant traumatic injury within 2 weeks prior to start of study treatment. Note: Minor procedures and percutaneous biopsies or placement of vascular access device require 7 days wash-out period prior to start of study treatment
9. Anticipation of the need for major surgical procedure during the course of the study
10. Radiation therapy within 4 weeks prior to start of study treatment (palliative radiotherapy to bone lesions allowed within 2 weeks prior to study treatment start)
12. History of severe hypersensitivity reactions to other monoclonal antibodies which in the opinion of the investigator may pose an increased risk of a serious infusion reaction.
13. Impaired cardiac function or clinically significant cardiac disease, including any of the following:

    Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (New York Heart Association (NYHA) grade ≥ 2)

    - Uncontrolled hypertension with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication is allowed prior to screening or clinically significant arrhythmia,
    - QTcF >480 ms on screening ECG or congenital long QT syndrome, acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry.
14. Autoimmune disease that has required systemic treatment (i.e. disease modifying agents, steroids, or immunosuppressive drugs). Stable and adequate controlled endocrinopathies requiring replacement therapy (i.e. thyroid hormones, insulin, or physiologic corticosteroids) are not considered as systemic treatment and therefore are allowed.
15. Active infection requiring systemic antibiotic therapy.
16. Known history of testing positive for Human Immunodeficiency Virus (HIV) infection.
17. Patients with active Hepatitis B infection (HBsAg positive) will be excluded.

    Note: Patients with prior Hepatitis B (anti-HBc positive, HBsAg and HBV-DNA negative) infection are eligible.
18. Patients with positive test for hepatitis C ribonucleic acid (HCV RNA).

    Note: Patients in whom HCV infection resolved spontaneously (positive HCV antibodies without detectable HCV-RNA) or those that achieved a sustained virological response after antiviral treatment and show absence of detectable HCV RNA ≥ 6 months (with the use of IFN-free regimes) or ≥ 12 months (with the use of IFN-based regimes) after cessation of antiviral treatment are eligible.
19. 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.

[redacted]

20. Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment.
21. Presence of ≥ CTCAE grade 2 toxicity (except alopecia, peripheral neuropathy, and ototoxicity, which are exclusion criteria if ≥ CTCAE grade 3) due to prior cancer therapy.
22. Not able to understand and to comply with study instructions and requirements.
23. Pregnant or nursing (lactating) women confirmed by a positive hCG laboratory test within 72 hours prior to initiating study treatment. Note: Low levels of hCG may also be considered a tumor marker, therefore if low hCG levels are detected, another blood sample at least 4 days later must be taken to assess the kinetics of the increase and transvaginal ultrasound must be performed to rule out pregnancy.
24. 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 stopping treatment with PDR001. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    c. Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient
    d. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

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

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

26. Known history or current interstitial lung disease or non-infections pneumonitis.
27. Use of somatostatin analogs or any other medications administered to control active symptoms related to carcinoid syndrome during the last 3 months prior to start of study treatment.

[redacted]

6 Treatment

6.1 Study treatment

For this study, the investigational drug is PDR001. The study treatment is defined as PDR001. PDR001 is supplied as PDR001 100 mg powder for solution for infusion. PDR001 will be diluted in dextrose 5% in water (D5W). Due to incompatibility, 0.9% sodium chloride solution must not be used. PDR001 will be administered at a dose of 400 mg every 4 weeks given as a 30 minute infusion.

PDR001 infusion must take place in a facility with appropriate resuscitation equipment available at the bedside and a physician readily available during the period of drug administration.

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

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Strength	Frequency and/or Regimen	Dose Administered
PDR001	Powder for solution for infusion in vial for i.v. infusion	4 x 100 mg vials	Every 4 weeks	400 mg

PDR001 will be administered via intravenous infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 4 weeks (+/- 7 days window). PDR001 will be administered on Day 1 of every cycle. Each cycle is 28 days. The actual date of Cycle Day 1 will be used to project the dates of future cycles. The dose may be interrupted for up to 12 weeks. The safety assessments (as per Table 7-1 and Section 7.2.2) should be performed according to the actual day of infusion.

6.1.2 Ancillary treatments

Patients should not receive pre-medication to prevent infusion reaction before the first infusion of PDR001 as a way to determine if pre-medication is necessary. If a patient experiences an infusion reaction, he/she may receive pre-medication prior to 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 severe anaphylactic/anaphylactoid reaction, the infusion should be discontinued immediately. The patient may only resume study treatment 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 Section 6.3.1.2.

[redacted]

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

6.1.3 Rescue medication

Not applicable

6.1.4 Guidelines for continuation of treatment

Not applicable

6.1.5 Treatment duration

All patients will begin treatment on Cycle 1 Day 1.

Prior to the primary analysis cut-off date (10-Aug-2018), patients will continue study treatment until disease progression per RECIST 1.1 or irRECIST (see below), **as per BIRC,** unacceptable toxicity, start of new anti-neoplastic therapy, withdrawal of consent, physician's decision, subject/guardian decision, lost to follow-up, death or the study is terminated by the sponsor. While the investigator is waiting for the results from the central imaging vendor to confirm disease progression, the patient should continue on study treatment. However, during this time, the investigator should do whatever is medically necessary for his/her patient.

After the primary analysis cut-off date (10-Aug-2018):

- Response assessments by BIRC will no longer be performed.
- Patients, who are on treatment but have not yet progressed per local tumor response assessment, will continue study treatment until documentation of disease progression by RECIST 1.1 as per local investigator assessment, unacceptable toxicity, start of new anti-neoplastic therapy, withdrawal of consent, physician's decision, subject/guardian decision, lost to follow-up, death or the study is terminated by the sponsor. These patients will be permitted to continue study treatment beyond initial PD as per RECIST 1.1 until confirmed irPD per local assessment (until 2 consecutive irPDs), as described in Section 6.1.5.1.
- Patients, who are on treatment beyond disease progression per local tumor response assessment (tumor assessment performed before the primary analysis cut-off date [10-Aug-2018]), are allowed to continue study treatment as long as the patient derives clinical benefit from the treatment according to investigator's best clinical judgement (e.g. no deterioration of performance status, no rapid increase in tumor burden, no clinical situation requiring alternative treatment), or until unacceptable toxicity, start of new anti-neoplastic therapy, withdrawal of consent, lost to follow-up, death, or the study is terminated by the sponsor.

6.1.5.1 Treatment beyond disease progression

Emerging clinical data indicate that patients may derive benefit from continuing study treatment despite initial evidence of disease progression (Section 2.5).

[redacted]

Prior to the primary analysis cut-off date (10-Aug-2018), patients treated with PDR001 will be permitted to continue study treatment beyond initial disease progression as per RECIST 1.1 until disease progression per irRECIST, as per BIRC, unacceptable toxicity, start of new anti-neoplastic therapy provided they meet all of the following criteria:

- Absence of disease progression per irRECIST, as per BIRC, confirmed by 2 consecutive assessments
- The continuation of treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
- Patients exhibit adequate tolerance to study treatment
- Patient performance status is stable

Patients who meet the above criteria should continue study treatment beyond initial disease progression per RECIST 1.1 and continue all study procedures as outlined in Section 7. The reasons for the patient continuing treatment will be documented in the eCRF.

In case of clinical deterioration or suspicion of disease progression, a follow-up imaging assessment should be performed promptly rather than waiting for the next scheduled assessment. Treatment with PDR001 in patients who are no longer deriving clinical benefit or have disease progression as per irRECIST by BIRC confirmed by 2 consecutive assessments must be discontinued.

After the primary analysis cut-off date (10-Aug-2018):

- Response assessments by BIRC will no longer be performed.
- Patients, who are on treatment but have not yet progressed per local tumor response assessment, will continue study treatment until documentation of disease progression by RECIST 1.1 as per local investigator assessment, unacceptable toxicity, start of new anti-neoplastic therapy, withdrawal of consent, physician's decision, subject/guardian decision, lost to follow-up, death or the study is terminated by the sponsor. These patients will be permitted to continue study treatment beyond initial PD as per RECIST 1.1 until confirmed irPD per local assessment (until 2 consecutive irPDs) provided they meet all of the following criteria:
  - Absence of disease progression per irRECIST, confirmed by 2 consecutive assessments
  - The continuation of treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
  - Patients exhibit adequate tolerance to study treatment
  - Patient performance status is stable
  - Patients who meet the above criteria should continue study treatment beyond initial disease progression per RECIST 1.1 and continue study procedures as outlined in Section 7. The reasons for the patient continuing treatment will be documented in the eCRF.
- Patients, who are on treatment beyond disease progression per local tumor response assessment (tumor assessment performed before the primary analysis cut-off date (10-Aug-2018)), are allowed to continue study treatment as long as the patient derives clinical benefit from the treatment according to investigator's best clinical judgement (e.g. no

[redacted]

deterioration of performance status, no rapid increase in tumor burden, no clinical situation requiring alternative treatment), or until unacceptable toxicity, start of new anti-neoplastic therapy, withdrawal of consent, lost to follow-up, death, or the study is terminated by the sponsor.

6.2 Dose escalation guidelines

Not applicable

6.3 Dose modifications

6.3.1 Dose modification and dose interruption

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions are mandated in order to allow patients to continue study treatment. Dose interruption for PDR001 includes delaying or withholding treatment for any reason as well as interrupting treatment during an infusion.

The following sections address specific instructions for mandatory dose modifications and recommended management of adverse events considered suspected to be related to PDR001.

6.3.1.1 Dose modification and dose interruption for PDR001

General dose modification instructions:

No changes in the dose of PDR001 are allowed.

AEs are to be graded according to NCI-CTCAE v4.03 (ctep.cancer.gov). All dose interruptions and the reasons for dose interruption must be documented in the eCRF.

Treatment of patients with AEs suspected to be related to PDR001 including those of potential immune-mediated etiology (irAE) (see definition in Section 6.3.1.2.1) must be permanently discontinued if the following occurs within 12 weeks:

- AEs do not recover to ≤ grade 1 or baseline
- The dose of steroids (for the management of irAEs) is > 10 mg/day prednisone or equivalent (or as indicated in the tables below)

The 12 weeks' period starts from the time an irAE reaches a severity grade that requires PDR001 interruption.

6.3.1.2 Dose Modification requirements for potential immune- mediated adverse events

6.3.1.2.1 Identification of and management requirements for AEs of potential immune-mediated etiology (irAE)

Adverse events of special interest (AESI) include AEs of a potential immune-mediated etiology (irAE) that are associated with PDR001 treatment. An irAE may be experienced by patients treated with PDR001 due to its mechanism of action; it is predicted based on the reported prior experience with other immunotherapies that have a similar mechanism of action. Investigators

[redacted]

must be vigilant and must carefully identify AEs that may be suggestive of potential irAEs as their appearance may be sub-clinical and early diagnosis is critical for its adequate management and resolution.

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), lung (pneumonitis), kidneys (nephritis) and endocrine systems (a variety of endocrinopathies) and rarely CNS (encephalitis). Serological, immunological and histological assessments should be performed as deemed appropriate by the investigator, to verify the potential immune-related nature of the AE, and exclude a neoplastic, infectious or metabolic origin of the AE.

Severe grade or persistent lower grade irAEs typically require interrupting or permanently discontinuing treatment and administration of systemic steroids or other non-corticosteroid immunosuppressive medication when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants.

Patients should be instructed to return to the study site as soon as possible (instead of waiting for their next scheduled visit) if they experience symptoms consistent with an irAE. Patients who experience a new or worsening irAE should be contacted and/or evaluated by the study site more frequently.

Based on literature from compounds with similar mechanism of action of PDR001, instructions have been developed regarding how to identify, assess severity and manage irAEs that may occur in patients receiving PDR001. The dose modification requirements and AE management guidelines for the potential irAEs are provided in the following tables: diarrhea/colitis (Table 6-2), hepatitis (liver laboratory alterations) (Table 6-3), skin (rash) (Table 6-4), nephritis (Table 6-5), pneumonitis (Table 6-6), encephalitis (Table 6-7), endocrinopathies (Table 6-8), PDR001-infusion reaction & cytokine release syndrome (Table 6-9), and other potential immune-related AEs of special interest (Table 6-10). Any grade 4 irAE must result in permanent discontinuation of PDR001.

Under the category of OTHERS (Table 6-11 and Table 6-12) are included several irAE of interest that must be managed specifically and for which not specific guidance are provided in the table below. OTHERS include (but is not restricted to) the following events: autoimmune neuropathy, demyelinating polyneuropathy, Guillain-Barre, myasthenia Gravis-like syndrome, non-infectious myocarditis, non-infectious pericarditis, pancreatitis and rapid onset of grade 3 fatigue in the absence of disease progression.

Patients receiving PDR001 may experience irAEs other than those listed in this document; therefore, all AEs of unknown etiology associated with drug exposure should be evaluated to determine if they are possibly immune-related. In cases where the specific irAEs are not listed in the tables below, the investigator should follow the dose modification requirements in Section 6.3.1.3 which details the measures to be taken for suspected (they could be potentially immune-related or non-immune-related) AEs. Investigators are encouraged to contact the sponsor as needed to discuss cases that warrant separate discussion outside of the scope of the current instructions.

[redacted]

The dosing modification requirements are mandatory; however, the AE management guidelines are recommendations and can be modified according to local practices. The management of irAEs may include initiation of antibiotics for prophylaxis against opportunistic infections.

Table 6-2 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related diarrhea/colitis

Diarrhea/Colitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 (< 4 bowel actions per day over baseline) mild Grade 2 (4-6 bowel actions per day over baseline) and / or abdominal pain/ blood in stool.	● Diet ● Hydration ● Loperamide: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours; ● Diarrhea > 24h: loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics. ● Diarrhea > 48hrs: loperamide 2 mg every two hours; maximum 16 mg/day. Consider other second-line therapies for diarrhea (e.g: (octreotide, oral diphenoxylate) and oral antibiotics ● If Grade 2 and no improvement in 5 days may require oral steroids ● If Grade 2 diarrhea persists >1 week consider GI consultation and endoscopy to evaluate for colitis. ● If Grade 2 persists for 5 days and worsening of symptoms or diffuse ulcerations and bleeding seen on endoscopy, commence steroids at a dose of 0.5-1mg/kg per day of prednisolone (or IV equivalent) and continue until symptoms improve to Grade 1. If no improvement occurs, manage as per Grade 3. Steroids can be tapered as per Section 6.3.1.2.2. ● Sigmoidoscopy and biopsy can be considered and may assist in determining the duration of steroid taper based on the evidence of macroscopic and microscopic inflammation.	● Continue PDR001 treatment ● If diarrhea is Grade 2, despite loperamide at 2 mg every two hours for > 48hrs: ● Interrupt PDR001 until diarrhea recovers to Grade ≤1 and then restart PDR001 treatment at the same dose and schedule.
Grade 3 Diarrhea: Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care ADL; Grade 3 Colitis: Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	● Clinical evaluation and hospitalization mandatory; rule out bowel perforation and intravenous hydration. ● Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. ● In addition to symptomatic treatment (diet, hydration, loperamide, antibiotics if indicated); initiate immediate treatment with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) is recommended. ● When symptoms improve to ≤Grade 1, steroid taper should be done as per Section 6.3.1.2.2. ● Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding. ● If no improvement in 2-3 days: consider initiating infliximab 5mg/kg and continue steroids. (Infliximab is contraindicated in patients with sepsis or a perforation). Upon symptomatic relief initiate a prolonged steroid taper over 45 to 60 days. ● If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.	1st occurrence: ● Interrupt PDR001 until diarrhea/colitis recovers to Grade ≤1 or baseline ● Once recovered restart PDR001 treatment at the same dose and schedule and after appropriate steroid tapering (if initiated). ● AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since a Grade 3 event has been identified, otherwise PDR001 must be permanently discontinued 2nd occurrence: Permanently discontinue PDR001

[redacted]

Diarrhea/Colitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	● If symptoms persist despite the above treatment a surgical consult should be obtained.	
Grade 4: Life-threatening consequences; urgent intervention indicated	Same as Grade 3	Permanently discontinue PDR001

Table 6-3 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related liver laboratory alterations

Abnormal liver function tests		
Severity	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 2: AST or ALT > 3x ULN to ≤ 5.0x ULN and/or bilirubin > 1.5x ULN to ≤ 3x ULN (if patient meets criteria for Hy's law, refer to Section 6.3.3.1)	Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values	● Interrupt PDR001 treatment until recovery to Grade ≤1 or baseline** ● Once recovered restart PDR001 treatment at the same dose and schedule
Grade 3 or 4: AST or ALT >5.0xULN and/or bilirubin > 3.0x ULN	● Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values. ● Consider appropriate consultation* with hepatologist and liver biopsy to establish etiology of hepatic injury, if necessary ● If after 2-3 days new liver assessment shows worsening of laboratory test consider to initiate treatment with steroids prednisolone 1-2 mg/kg/day or IV equivalents. ● Add prophylactic antibiotics for opportunistic infections ● When symptoms improve to Grade ≤1, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks. ● If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. ● Infliximab is not recommended due to its potential for hepatotoxicity	Permanently discontinue PDR001**

* Send viral serology looking for hepatitis A, B, C & CMV and rule out any potential cause of liver injury (i.e. alcohol, other medications, etc.)
**For patients with liver metastasis who begin treatment with grade 2 AST or ALT, if AST or ALT increase by 2 times relative to baseline and last for at least 1 week then the patient should be discontinued
Note: For additional information on follow-up of potential drug induced liver injury cases, refer to Section 6.3.3.1.

[redacted]

Table 6-4 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related skin events

Rash Events (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1: Rash covering < 10% Body Surface Area (BSA)	● Initiate prophylactic and symptomatic treatment measures. ● Consider use of topical corticosteroids or urea containing creams in combination with oral antipruritics or moderate strength topical steroid (hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) ● Reassess after 2 weeks.	Continue PDR001 treatment
Grade 2: 10-30% of BSA	● If tolerable, treat as per Grade 1; ● If intolerable, initiate systemic steroids (e.g. oral prednisolone 0.5-1mg/kg daily) and consider dose interruption until tolerable or recovery to grade ≤1 or baseline; once recovered, resume PDR001 treatment at the same dose and schedule. ● If symptoms persist or recur consider skin biopsy.	Continue PDR001 treatment AE resolution to ≤1 or baseline must occur within a period of 12 weeks since Grade 2 event has been identified, otherwise PDR001 must be permanently discontinued.
Grade 3: More than 30% of BSA	● Obtain a skin biopsy and dermatology consult. ● Initiate systemic steroids with 1mg/kg of prednisolone or IV equivalent.	1st occurrence: ● Interrupt PDR001 until rash recovers to Grade ≤1 or baseline ● Once recovered restart PDR001 treatment at the same dose and schedule AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since intolerable Grade 3 event has been identified. Otherwise, PDR001 must be permanently discontinued 2nd occurrence: Permanently discontinue PDR001
Grade 4: Life-threatening	Same as Grade 3	Permanently discontinue PDR001
Other skin events		
Stevens-Johnson syndrome and toxic epidermal necrolysis	Institute supportive care as per institutional guidelines	Permanently discontinue PDR001

Table 6-5 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related nephritis

Nephritis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1: Creatinine >ULN to ≤1.5x ULN)	● Monitor creatinine weekly ● If creatinine return to baseline resume routine creatinine monitoring per protocol ● Promote hydration and cessation of nephrotoxic drugs	Continue PDR001 treatment
Grade 2: Creatinine >1.5 to ≤3 x ULN	● Monitor creatinine every 2 to 3 days ● Initiate 0.5 to 1 mg/kg/day prednisone equivalents ● If worsening or no improvement: 1 to 2 mg/kg/day prednisone equivalents ● Consult with specialist and consider renal biopsy	● Interrupt PDR001 until serum creatinine recovers to ≤ Grade 1 or baseline. ● Once recovered restart PDR001 treatment at the same dose and schedule AE resolution to ≤ Grade 1 must occur within a period of 12 weeks since Grade 2 event has been identified, otherwise PDR001 must be permanently discontinued.
Grade 3: Creatinine >3.0 to <6 x ULN	● Monitor creatinine every 1 to 2 days ● Start 1 to 2 mg/kg/day prednisone equivalents ● Consult with nephrologist	1st occurrence: ● Interrupt PDR001 until serum creatinine recovers to ≤Grade 1 or baseline. ● Once recovered restart PDR001 treatment at the same dose and schedule AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since the Grade 3 event has been identified, otherwise PDR001 must be permanently discontinued 2nd occurrence: Permanently discontinue PDR001.
Grade 4: Creatinine >6x ULN	● Monitor creatinine daily ● Initiate steroids with 1 to 2 mg/kg/day prednisone or equivalent ● Consult with nephrologist and consider renal biopsy	Permanently discontinue PDR001

Table 6-6 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related pneumonitis

Pneumonitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1: Radiographic changes only- Asymptomatic	● CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression- re-image at least every 3 weeks ● Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-	● Interrupt PDR001 until recovery to baseline. ● Once recovered, restart PDR001 treatment at the same dose and schedule If worsens, treat as Grade 2 or 3-4.

[redacted]

Pneumonitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	up for infection ● Monitoring of oxygenation via pulse oximetry recommended ● Consultation of pulmonologist recommended	AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since Grade 1 event has been identified, otherwise PDR001 must be permanently discontinued
Grade 2: Symptomatic-medical intervention indicated; limits instrumental ADLs	● CT scan (high-resolution with lung windows) ● Monitor symptoms daily, consider hospitalization ● Clinical evaluation and laboratory work up for infection ● Consult pulmonologist ● Pulmonary function tests - if normal at baseline, repeat every 8 weeks ● Bronchoscopy with biopsy and/or BAL recommended ● Symptomatic therapy including corticosteroids if clinically indicated (systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated).	1st occurrence: ● Interrupt PDR001 until recovery to Grade ≤1 or baseline ● Once recovered restart PDR001 treatment at the same dose and schedule AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since Grade 2 event has been identified, otherwise PDR001 must be permanently discontinued. If worsens treat as Grade 3 or 4 2nd occurrence: Permanently discontinue PDR001 treatment
Grade 3: Severe symptoms; limits self-care ADLs; oxygen indicated Grade 4: Life-threatening respiratory compromise	● CT scan (high-resolution with lung windows) ● Clinical evaluation and laboratory work-up for infection ● Consult pulmonologist ● Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal ● Bronchoscopy with biopsy and/or BAL if possible ● Treat with intravenous steroids (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours). ● If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication.	Permanently discontinue PDR001

Table 6-7 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related encephalitis

Encephalitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 (asymptomatic or mild symptoms)		Continue PDR001 treatment
Grade 2 (New onset of moderate	● Consider consulting neurology ● 0.5 to 1 mg/kg/day prednisone equivalents	1st occurrence: ● Interrupt PDR001 until recovery to ≤ Grade 1 or baseline.

[redacted]

Encephalitis (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
symptoms, limiting instrumental ADL)		● Once recovered restart PDR001 treatment at the same dose and schedule. AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since Grade 2 event has been identified, otherwise PDR001 must be permanently discontinued. If worsens, treat as Grade 3-4 2nd occurrence: Permanently discontinue PDR001
Grade 3 or 4 (New onset of severe symptoms, limiting self-care ADL, life-threatening)	● Consider consulting neurology ● 1 to 2 mg/kg/day prednisone equivalents	Permanently discontinue PDR001

Table 6-8 Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related endocrine events

Endocrine events (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Asymptomatic, intervention not indicated (e.g. hyperthyroidism or hypothyroidism)	● If TSH <0.5x LLN, or TSH >2x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated ● Consider endocrinologist consult ● If hypophysitis is considered, pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis) ● Repeat labs in 1 to 3 weeks/MRI in 1 month if laboratory abnormalities persist but normal lab/pituitary scan	Continue PDR001 treatment
Symptomatic endocrinopathy (e.g., hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)	● Consider Endocrinology consultation ● Rule out infection and sepsis with appropriate cultures and imaging ● Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. ● Replacement of appropriate hormones may be required as the steroid dose is tapered ● Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis ● Consider hospitalization and intravenous methylprednisolone should be initiated.	1st occurrence: ● Interrupt PDR001 until symptomatic recovery to mild (e.g. grade 1) or no symptoms ● Once recovered, restart PDR001 treatment at the same dose and schedule AE resolution to mild or no symptoms must occur within a period of 12 weeks since symptomatic endocrinopathy event has been identified, otherwise PDR001 must be permanently discontinued.

[redacted]

Endocrine events (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
		2nd occurrence: Permanently discontinue PDR001
Autoimmune diabetes (Grade 3 or symptomatic hyperglycemia)	Initiate anti-glycemic therapy (i.e. insulin) as medically indicated and monitor glucose levels regularly until metabolic control is achieved	Interrupt treatment until glucose returns to Grade 1 or baseline and then restart PDR001
Autoimmune diabetes (Grade 4 hyperglycemia or life-threatening complications)	Same as Grade 3	Permanently discontinue PDR001

Table 6-9 Mandatory dose modification requirements and recommended clinical management guidelines for infusion reaction events and cytokine release syndrome

Infusion reaction (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	Continue PRD001 treatment
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	● Stop Infusion ● Additional appropriate medical therapy may include but is not limited to: ● IV fluids ● Antihistamines ● NSAIDS ● Acetaminophen ● Narcotics ● Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. ● If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be re-premedicated for the next scheduled dose. ● Patient may be premedicated 1.5hr (± 30 minutes) prior to infusion of PDR001 with: ● Diphenhydramine 50 mg po (or equivalent dose of antihistamine). ● Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).	1st occurrence: Continue PRD001 treatment at the same dose and schedule with premedication 2nd occurrence: Despite premedication or prolongation of infusion, consider permanent discontinuation of PDR001.
Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement;	● Stop Infusion ● Additional appropriate medical therapy may include but is not limited to: ● IV fluids ● Antihistamines ● NSAIDS ● Acetaminophen ● Narcotics	Permanently discontinue PDR001

[redacted]

Infusion reaction (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	● Oxygen ● Pressors ● Corticosteroids ● Epinephrine ● Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	

Table 6-10 Mandatory dose modification requirements and recommended clinical management guidelines for "other" potential immune-related AEs of special interest

Other- Autoimmune neuropathy, demyelinating polyneuropathy, Guillain Barre, Myasthenia Gravis- like syndrome, Non-infectious myocarditis, pericarditis, pancreatitis, and Grade 3 Fatigue with rapid onset in absence of disease progression		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Mild (Grade 1)	Provide symptomatic treatment	Continue PDR001 treatment
Moderate (Grade 2) or Grade 1 that does not improve with symptomatic treatment	● Provide symptomatic treatment ● Systemic corticosteroids may be indicated ● Consider biopsy for confirmation of diagnosis ● A specialist should be consulted	1st occurrence: ● Interrupt PDR001 until recovery to ≤ Grade 1 or baseline. ● Once recovered, may restart PDR001 treatment at the same dose and schedule AE resolution to ≤ Grade 1 or baseline must occur within a period of 12 weeks since event has been identified, otherwise PDR001 must be permanently discontinued. 2nd occurrence: Permanently discontinue PDR001
Severe (Grade 3)	● All management for moderate irAEs and ● Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg QD	1st occurrence: ● Interrupt PDR001 until recovery to ≤ Grade 1 or baseline ● May restart PDR001 treatment at the same dose and schedule AE resolution to ≤ Grade 1 or baseline must occur within a maximum period of 12 weeks since a Grade 3 event has been identified, otherwise PDR001 must be permanently discontinued. 2nd occurrence: Permanently discontinue PDR001
Grade 4	Refer to management of severe AEs	Permanently discontinue PDR001.

[redacted]

6.3.1.2.2 Guidance for corticosteroids tapering for management of immune-related AEs

Reduce prednisone dose by 2.5- to 5.0-mg decrements every 3–7 days until physiologic dose (5 to 7.5 mg of prednisone per day) is reached. Consider to complete tapering over a period of at least 4 weeks. Slower tapering of corticosteroids therapy may be recommended if the adverse event is not showing improvement. Once corticosteroid tapering is achieved at a level of 10 mg of prednisone/day (or equivalent), treatment with PDR001 can be restarted as indicated in the dose modification tables.

6.3.1.3 Dose modification requirements for adverse events suspected to be related to study treatment

The required dose modification and management of adverse events that are considered to be related to study medication and do not have specific management requirements noted elsewhere in the protocol are provided in Table 6-11 and Table 6-12.

Table 6-11 Mandatory dose modification requirements and recommended clinical management guidelines for hematologic adverse events suspected to study treatment

Hematologic suspected AEs (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Neutropenia		
Grades 1, 2	NA	Continue PDR001 treatment
Grade 3, 4	Monitoring blood test more frequently (every 7 days for grade 3, and 3-5 days for grade 4)	1st occurrence: ● Interrupt PDR001 until toxicity recovers to Grade ≤2 or baseline. ● Once recovered restart PDR001 treatment at the same dose and schedule 2nd occurrence: ● Interrupt PDR001 until toxicity recovers to Grade ≤2 or baseline ● Once recovered restart PDR001 treatment at the same dose and schedule AE resolution to ≤ Grade 2 or baseline must occur within a maximum period of 12 weeks since Grade 3 or 4 event has been identified, otherwise PDR001 must be permanently discontinued 3rd occurrence: Permanently discontinue PDR001.
Febrile Neutropenia	Apply Institutional guidelines	Follow- neutropenia Grade 4 requirements (above)
Thrombocytopenia (NCI-CTCAE v4.03)		
Grade 1, 2, 3 without clinical significant bleeding	Grade 3: monitoring blood test more frequently (every 7 days)	Continue PDR001 treatment

[redacted]

Hematologic suspected AEs (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 3 with clinical significant bleeding OR Grade 4	Grade 3: monitoring blood test more frequently (every 3-5 days)	1st occurrence: ● Interrupt PDR001 until toxicity resolves to Grade ≤2 or baseline. ● Once recovered restart PDR001 treatment at the same dose and schedule 2nd occurrence: ● Interrupt PDR001 until toxicity resolves to Grade ≤2 or baseline ● Once recovered restart PDR001 treatment at the same dose and schedule AE resolution to ≤ Grade 2 or baseline must occur within a maximum period of 12 weeks since Grade 3 with clinically significant bleeding or Grade 4 event has been identified, otherwise PDR001 must be permanently discontinued. 3rd occurrence: Permanently discontinue PDR001.

Table 6-12 Mandatory dose modification requirements and recommended clinical management guidelines for non-hematologic adverse events suspected related to study treatment

Non-Hematologic suspected AEs (except Grade 2 alopecia, Grade 2 fatigue) (NCI-CTCAE v4.03)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1-2 tolerable	● Monitor closely ● Provide supportive care according to institutional standards	Continue PDR001 treatment at the same dose and schedule
Grade 2 intolerable or Grade 3	● Monitor closely ● Provide supportive care according to institutional standards	1st or 2nd occurrence: ● Interrupt PDR001 until toxicity recovers to Grade ≤1 or baseline. ● Once recovered restart PDR001 treatment at the same dose and schedule AE resolution to Grade ≤1 or baseline must occur within a maximum period of 12 weeks since intolerable Grade 2 or Grade 3 event has been identified, otherwise PDR001 must be permanently discontinued. 3rd occurrence: Permanently discontinue PDR001
Grade 4	● Monitor closely ● Provide supportive care according to institutional standards	1st occurrence: ● Interrupt PDR001 ● Consider permanently discontinuing PDR001. If benefit risk assessment support treatment continuation, restart PDR001 treatment at the same dose and schedule. 2nd occurrence: Permanently discontinue PDR001

[redacted]

6.3.2 Dose adjustments for QTcF prolongation

Not applicable

6.3.3 Follow-up for toxicities

Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator to verify the immune-related nature of the AE and to exclude alternative explanations. Recommendations (Section 6.3) have been developed to assist investigators in assessing and managing the most frequently occurring irAEs.

Patients whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 30 days, and subsequently at approximately 30-day intervals (or more frequently if required by institutional practices, or if clinically indicated), until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

If an AE is suspected to be immune-related, the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed. If cytokine release syndrome is suspected, the assessments outlined in Section 7.2.6.6.5 must be performed.

All patients must be followed-up for AEs and SAEs for 150 days following the last dose of PDR001. However, if the patient begins post-treatment antineoplastic medication during the period between the 30-Day safety follow-up and 150-Day safety follow-up, the collection of new SAEs and AEs unrelated to study medication will stop, and thereafter only suspected SAEs and suspected AEs will continue to be collected to Day 150. If SAEs suspected to be related to study medication occur beyond Day 150, information should also be collected. Section 6.3.3.1 outline the follow-up evaluations recommended for selected toxicities.

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

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

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

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

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

[redacted]

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

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

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

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

6.4 Concomitant medications

6.4.1 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 except those prohibited in Section 6.4.3. The following list includes permitted concomitant therapies:

- Medications to prevent or treat nausea or vomiting.
- Anti-diarrheal medications (e.g., loperamide) for patients who develop diarrhea.
- Pain medication to allow the patient to be as comfortable as possible.
- Localized radiotherapy and treatment with bisphosphonates for pre-existing, painful bone/liver metastases is permitted. The radiotherapy must be listed on the CRF.
- Immunosuppressive agents to treat suspected irAEs.
- Nutritional support or appetite stimulants (e.g. megestrol).
- Oxygen therapy and blood products or transfusions.
- Limited-field palliative radiotherapy may be allowed as concomitant therapy. Such local therapies administered during the study treatment must be listed on the CRF.

[redacted]

- Inactivated vaccines.
- The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications.

6.4.2 Permitted concomitant therapy requiring caution and/or action

If a patient is using erythropoiesis stimulating agents (ESAs) prior to enrollment (at least 2 weeks before start of study treatment), he/she may continue the treatment.

Anticoagulation and anti-aggregation agents are permitted if the patients are already at stable doses 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.

6.4.3 Prohibited concomitant therapy

During the course of the study, patients must not receive other additional investigational drugs, devices, chemotherapy, or any other therapies that may be active against cancer or modulate the immune responses. However, limited-field palliative radiotherapy may be allowed as concomitant therapy. Such local therapies administered during the study treatment must be entered into the CRF. Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication may be administered while on this study unless given for the management of immune toxicity.

The use of somatostatin analogs or any other medications administered to control active symptoms related to carcinoid syndrome is not permitted during the study unless there is a change to functional status (Section 6.4.4.1).

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of infusion reaction, irAEs, and for prophylaxis against imaging contrast dye allergy or 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 COPD requiring treatment for ≤ 3 weeks. If systemic corticosteroids are required for the control of infusion reactions or irAEs, it must be tapered and be at non-immunosuppressive doses (< 10 mg/day of prednisone or equivalent) before the next administration of study treatment. If the dose of prednisone or equivalent cannot be reduced to less than 10 mg/day before the administration of next dose of study treatment then PDR001 must be discontinued.

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

There are no prohibited therapies during the post-treatment follow-up period.

[redacted]

6.4.4 Use of bisphosphonates (or other concomitant agents)

Localized radiotherapy and treatment with bisphosphonates for pre-existing, painful bone/liver metastases is permitted. The radiotherapy must be listed on the concomitant Antineoplastic Therapy – Radiotherapy CRF.

6.4.4.1 Proposed language for other concomitant medications

The use of somatostatin analogs is permitted to control symptoms which are developed on study in patients with neuroendocrine tumors changing to functional status.

6.5 Patient numbering, treatment assignment

6.5.1 Patient numbering

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

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 Subject No. must not be reused for any other patient and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient was not treated as scheduled.

6.5.2 Medication number assignment

All patients who fulfill all inclusion/exclusion criteria will be assigned to be treated with PDR001. No randomization will be performed in this study.

IRT will be used to assign a medication number for each PDR001 dose. The assignment of a patient to a particular cohort/group (pancreatic, GI, thoracic or GEP-NEC) will be coordinated and monitored by the sponsor.

6.5.3 Treatment blinding

Not applicable

6.6 Study drug preparation and dispensation

The dose administered to the patient and any study drug interruptions during the study must be recorded on the Dosage Administration Record CRF.

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

[redacted]

PDR001 will be administered intravenously as a 30 minute infusion (up to 2 hours, if clinically indicated). Clinical monitoring, during and post infusion, should be performed according to local practice and institutional guidelines. Further instructions for the preparation and dispensation of PDR001 are described in the [Study Pharmacy Manual].

6.6.1 Study treatment packaging and labeling

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

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength). Responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the patient. Site personnel will add the patient number on the label. If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

6.6.2 Drug supply and storage

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

Table 6-13 Supply and storage of study treatments

Study treatments	Supply	Storage
PDR001	Centrally supplied by Novartis	Refer to study treatment label

6.6.3 Study drug compliance and accountability

6.6.3.1 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. Study drug interruptions of PDR001 must be specifically documented in the patient source documents and eCRF.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

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.

[redacted]

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 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 lists all of the assessments and indicates with an "X", when the visits are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

Table 7-1 also lists all changes in assessments after cut-off date of primary analysis (10-Aug-2018).

No paper CRF will be used as a source document.

PRO data will be captured on an ePRO tablet and is considered the source document.

Allowed visit windows are specified as follows:

Visit name	Window
Screening A serum pregnancy test (local Lab)	-28 days ≤ 72 hours before first dose of study treatment
Enrollment and Cycle 1 Day 1	None (should occur on the same day)
Hematology, chemistry, coagulation, Chromogranin A (CgA), neuron specific enolase (NSE) and urinalysis for Cycle 1 Day 1	≤ 4 days before first dose of study treatment
Day 1 of subsequent cycles	± 7 days
PK sampling	None (end-of-infusion samples should be collected within 30 min post infusion)
Scans	± 7 days (during treatment/follow-up)
PRO	± 7 days (during treatment/follow-up)
EOT	+ 7 days from the last PDR001 dose
30-Day safety follow-up visit	± 7 days
60-, 90-, 120-Day safety follow-up phone call/ visit	± 7 days
150-Day safety follow-up phone call or visit (visit for women of child-bearing potential (WOCBP) and phone call for all others) (Section 7.1.7)	± 14 days
Survival follow up	± 14 days

Every effort should be made to follow the schedule outlined in Table 7-1.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
Obtain Informed Consent	D	11.3	X										
[redacted]													
Patient history													
Demography	D	7.1.2.3	X										
Inclusion/exclusion criteria	D	5	X										
HIV history	S	5.3	X										
Medical history	D	7.1.2.3	X										
Diagnosis and extent of cancer	D	7.1.2.3	X										
Proliferative activity assessment	D	7.1.2.	X										
Presence of Necrosis	D	7.1.2.	X										

[redacted]

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
Prior antineoplastic therapy	D	7.1.2.3	X										
Prior/concomitant medications	D	7.1.2.3	X	From 30 days prior to starting study treatment until 150-Day safety follow-up or start of new antineoplastic medication, whichever is sooner. If new antineoplastic medication is started then only medications relative to the suspected AEs/SAEs that are reported should be collected.									
Prior/concomitant procedures and Significant Non-Drug Therapies	D	7.1.2.3	X	Continuous									
Enrollment													
Eligibility checklist (Contact IRT)	S	7.1.2.1	X										
Drug Supply (Contact IRT)	S	6.5	X	X	X	X							
Disposition Assessment (at the end of each study phase)	D		X			X						X	
Physical examination													
Physical examination	S	7.2.6.1	X	X	X	X	X						

[redacted]

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
ECOG Performance status	D	7.2.6.4	X	X	X	X	X						
Height	D	7.2.6.3	X										
Weight	D	7.2.6.3	X	X	X	X	X						
Vital signs	D	7.2.6.2	X	X	X	X	X						
Change in functional status of carcinoid syndrome	D	7.2.6.5	If applicable										
Laboratory assessments													
Hematology	D	7.2.6.6.1	X	X	X	X	X						
Chemistry	D	7.2.6.6.2	X	X	X	X	X						
Thyroid Panel- TSH	D	7.2.6.6.3	X		X	X	X						
Thyroid Panel- Free T3 and Free T4	D	7.2.6.6.3	X	Only if TSH is abnormal									
Coagulation	D	7.2.6.6.4	X	From Cycle 1 Day 1, every 8 weeks for		If clinically indicated	If clinically indicated						

[redacted]

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
				the first 13 cycles and every 12 weeks thereafter									
Urinalysis (microscopic or macroscopic)	S	7.2.6.6	X	X	X	X	X						
Urine pregnancy test	S	7.2.6.6.8			X			X	X	X			
Serum pregnancy test	D	7.2.6.6.8	X			X	X				X		
Hepatitis testing	D	7.2.6.6.6	X	If clinically indicated, perform testing as needed									
Cytokine for safety	D	7.2.6.6.5	X	Anytime when a suspected cytokine release syndrome occurs, immediately after the AE, and one week after occurrence of the AE									
CgA and NSE levels	D	7.2.6.6.7	X	X	X	X							
Imaging													
Tumor evaluation per RECIST 1.1 and irRECIST	D	7.2.2	X	**Before the primary analysis cut-off date (10-Aug-2018):** **Treatment Period:** Every 8 weeks counting from Cycle 1 Day 1 for the first 13 cycles and then every 12 weeks from Cycle 13 Day1 thereafter **EOT:** If a scan was not conducted within 30 days prior to end of study treatment									

[redacted]

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
				Efficacy follow-up: Continue same schedule as during treatment period until BIRC confirmed irRECIST progression **After the primary analysis cut-off date (10-Aug-2018)**: **Treatment Period:** scheduled according to local or institutional standards of care and when clinically indicated, and continue until locally-determined disease progression (per RECIST 1.1 or irRECIST). **EOT:** no scan needs to be perfomed at EOT **Efficacy follow-up:** Post-treatment efficacy follow-up will no longer be performed.								
Chest, abdomen and pelvis CT or MRI (with iv contrast)	D	7.2.2	X	**Before the primary analysis cut-off date (10-Aug-2018):** **Treatment Period:** Every 8 weeks counting from Cycle 1 Day 1 for the first 13 cycles and then every 12 weeks from Cycle 13 Day1 thereafter **EOT:** If a scan was not conducted within 30 days prior to end of study treatment **Efficacy follow-up:** Continue same schedule as during treatment period until BIRC confirmed irRECIST progression **After the primary analysis cut-off date (10-Aug-2018)**: **Treatment Period:** scheduled according to local or institutional standards of care and when clinically indicated, and continue until locally-determined disease progression (per RECIST 1.1 or irRECIST). **EOT:** no scan needs to be perfomed at EOT **Efficacy follow-up:** Post-treatment efficacy follow-up will no longer be performed.								

[redacted]

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
Brain CT or MRI	D	7.2.2	X	If positive at screening, follow same schedule as CT/MRI of chest, abdomen, and pelvis and if clinically indicated									
Whole body bone scan	D	7.2.2	If clinically indicated										
Localized bone CT, MRI or x-ray	D	7.2.2	Only for lesions on whole body scan that are not visible on the chest, abdomen and pelvis scans. If lesions were documented at screening, follow same schedule as CT/MRI of chest, abdomen, and pelvis										
12-lead ECG	D	7.2.6.7.1	X	From Cycle1 Day1, every 12 weeks		X	If clinically indicated						
Safety													
Adverse events	D	8.1	● Suspected AEs up to 150-Day safety follow-up ● Non-suspected AEs up to 150-Day safety follow-up or start of new post treatment anti-neoplastic medication if administered during the period between the 30-Day safety follow-up and 150-Day safety follow-up, whichever is sooner										
Serious Adverse Events	D	8.2	● Suspected SAEs up to 150-Day safety follow-up and beyond										
			● Non-suspected SAEs up to 150-Day safety follow-up or start of new post treatment anti-neoplastic medication if administered during the period between the 30-Day safety follow-up and 150-Day safety follow-up, whichever is sooner										

[redacted]

[redacted]

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
[redacted]													

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
			available visit)										
[redacted]													
Patient-reported Outcomes													
EORTC QLQ-C30	D	7.2.10	X		**Before the primary analysis cut-off date (10-Aug-2018):** **Treatment Period:** Every 8 weeks from Cycle 3 Day 1 for the first 13 cycles and every 12 weeks from Cycle 13 Day1 thereafter **EOT:** Collect at EOT Visit **30-day SafetyVisit:** Collect at 30-Day Safety Follow-up Visit **Efficacy follow-up:** Continue same schedule as during treatment period until BIRC confirmed irRECIST progression								

[redacted]

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
					After the primary analysis cut-off date (10-Aug-2018): ePROs collection will no longer be performed.								
EQ-5D-5L	D	7.2.10	X		**Before the primary analysis cut-off date (10-Aug-2018):** **Treatment Period:** Every 8 weeks from Cycle 3 Day 1 for the first 13 cycles and every 12 weeks from Cycle 13 Day1 thereafter **EOT:** Collect at EOT Visit **30-day SafetyVisit:** Collect at 30-Day Safety Follow-up Visit **Efficacy follow-up:** Continue same schedule as during treatment period until BIRC confirmed irRECIST progression **After the primary analysis cut-off date (10-Aug-2018):** ePROs collection will no longer be performed								
Study Drug Administration													
Study Drug administration	D			X									
Verification for treatment beyond RECIST 1.1	D	6.1.5.1		X									

[redacted]

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
progression (if necessary)													
Blood sampling for PK	D	7.2.7		**<u>Before</u> the primary analysis cut-off date (10-Aug-2018):** **Treatment period:** At Day 1 of all cycles until Cycle 13 and Day 1 of every 6 cycles thereafter until Cycle 25 **EOT** **30-Day safety follow-up** **150-Day safety follow-up for WOCBP** **Unscheduled:** At the time of PD based on RECIST 1.1 At the time of PD based on irRECIST **<u>After</u> the primary analysis cut-off date (10-Aug-2018):** No additional PK samples will be collected for the patients still ongoing on the study, unless requested by the Investigator.								
Immunogenicity (IG) sampling	D	7.2.7		**<u>Before</u> the primary analysis cut-off date (10-Aug-2018):** **Treatment period:** At Day 1 of all cycles until Cycle 13 and Day 1 of every 6 cycles thereafter until Cycle 25 **EOT** **30-Day safety follow-up** **150-Day safety follow-up for WOCBP** **Unscheduled:**								

[redacted]

	Category	Protocol Section	Screening period	Treatment period (cycle = 28 days)			Follow-up period						
			Screening	Cycle 1 Day 1	Subsequent cycles Day 1	EoT	30-Day Safety follow-up Visit	60-Day Safety follow-up phone call	90-Day Safety follow-up phone call	120-Day Safety follow-up phone call	150-Day safety follow-up visit / phone call (visit for WOCBP and phone call for all others)	End of post treatment follow-up	Survival F/U (after safety and efficacy follow-up)
Day of cycle			**-28 to -1**	**1**	**1**								**Every 3 months**
				At the time of PD based on RECIST 1.1 At the time of PD based on irRECIST At the time of suspected irAEs **<u>After</u> the primary analysis cut-off date (10-Aug-2018):** No additional IG samples will be collected for the patients still ongoing on the study, unless requested by the Investigator.								
Follow-up													
Survival follow-up		7.1.9											X
Antineoplastic therapies since discontinuation of study treatment	D	7.1.9				X	X	X	X	X	X		X

[redacted]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

Patients with non-functional, well-differentiated grade 1 or 2, progressing NETs of pancreatic, GI or thoracic (lung or thymic) origin or patients with poorly-differentiated GEP-NEC will be screened for eligibility during a maximum period of 28 days (Day -28 to Day -1) immediately prior to starting PDR001 on study Day 1. During this time, the inclusion and exclusion criteria will be assessed, and all screening assessments will be performed according to Table 7-1. Tumor tissue must be sent to a central laboratory within the screening timeframe as per eligibility criteria defined in Section 5.

The tumor pathology report must be verified by the study investigator to confirm histology and grade of neuroendocrine tumor (including mitotic count, Ki-67 index, and absence or presence of necrosis, as applicable). Data from previous tumor assessments (i.e. imaging scans) performed as part of the patient's routine care (prior to enrolling in the trial) must be considered to fulfill eligibility criteria #6 (Section 5.2). Patient eligibility will be checked once all screening procedures are completed. Results of all screening evaluations must be reviewed by the investigator prior to enrollment into the study, in order, to assure that all inclusion and exclusion criteria have been satisfied. Only laboratory results from the central laboratory can be used to determine patient eligibility.

An eligibility review and confirmation will be embedded in the IRT system. Please refer to and comply with detailed guidelines in the IRT manual. The IRT system will confirm the inclusion of eligible patients.

If a patient completed all screening evaluations and did not meet eligibility criteria, the patient is a screen failure. However, the investigator may choose to re-screen the patient. If the investigator chooses to re-screen the patient, the patient must sign a new ICF. All required screening evaluations must be performed again during re-screening; all re-screening evaluations must be performed within 28 days prior to the start of study treatment. Re-screening is allowed once per patient as long as the patient was not assigned a medication number for first dose by IRT. In this case the "Patient number" assigned to the patient initially will be used, and the patient will be identified by this number throughout his/her entire participation to the study. All re-screened evaluations must meet the eligibility criteria for the patient to receive treatment. If the patient completes all re-screening evaluations and still do not meet eligibility criteria, the patient is a screen failure.

For central laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted when initial results are out of the permitted range. In this case, the patient will not be required to sign another ICF, and the original patient ID number assigned by the investigator will be used. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure.

[redacted]

Once the number of patients screened and enrolled is likely to ensure target enrollment in a cohort or the study, the sponsor will close the cohort or the study to further screening. In this situation, patients who screen failed will not be permitted to be re-screened.

7.1.2.1 Eligibility screening

Once a patient is registered in the IRT for screening, patient eligibility will be checked after all screening procedures are completed. The eligibility checklist is embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

A patient who signed an Informed Consent Form but did not start treatment for any reason will be considered a screen failure.

The data from a screen failure patient will be entered on the Screening Phase Disposition Page.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for screen failures patients, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details).

7.1.2.3 Patient demographics and other baseline characteristics

Data will be collected on patient characteristics including:

- Demographic information (age, sex, race, height and weight),
- Other background or relevant medical history, including HIV history, cancer, disease baseline characteristics (diagnosis, history, and extent of cancer, prior anticancer therapies including surgery and local therapies such as radiotherapy), and
- Any other assessments that are done for the purpose of determining eligibility for inclusion in the study (i.e., ECOG Performance Status, complete physical examination, vital signs, hematology, blood chemistries including coagulation studies and urinalysis, pregnancy test only required for women of child-bearing potential, tumor imaging assessments, ECG, etc.).

All medications and significant non-drug therapies taken within 30 days prior to start of study treatment must be recorded on the Concomitant medication eCRF page and updated on a continual basis if there are any new changes to the medications.

Tumor imaging assessments will be performed for screening purposes and for determination of patient eligibility. Results of scans (as described in Table 7-2) performed within 28 days prior to start of study treatment will also be used as baseline values, except for whole body bone scans (if applicable, for suspected or known bone metastases), which can be performed within 6 weeks of start of study treatment. Chest, abdomen, and pelvis CT or MRI scans and brain CT or MRI scan are required to be performed at screening. See Section 7.2.1 Efficacy assessments for more details.

To determine eligibility, measurable and non-measurable lesions must be assessed. Target lesions must be identified prior to start of treatment. For definition of measurable and target lesions, please refer to Appendix 1.

[redacted]

7.1.3 Run-in period

Not applicable

7.1.4 Treatment period

Patients will start PDR001 intravenous infusion at a flat dose of 400 mg every 4 weeks on Cycle 1 Day 1 and continue dosing until any of the criteria for study treatment discontinuation is met (Section 4.1). Patients will visit the site on Day 1 of each cycle (1 cycle = 28 days) or more frequently, if medically indicated. For details on study procedures during treatment, please see Table 7-1 Visit evaluation schedule.

7.1.5 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 understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

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

Patients may stop study treatment for any of the following reasons:

- Adverse event(s)
- Progressive Disease
- Protocol Deviation
- Technical problems
- Physician decision
- Subject/guardian decision

Patients must stop study treatment for any of the following reasons:

- Death
- Pregnancy
- Study terminated by sponsor
- Lost to follow-up

Patients who discontinue study treatment should not be considered withdrawn from the study. They should undergo an end of treatment visit and then enter the safety, efficacy, and survival follow-up periods. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, and letter) should be made to contact them as specified in Section 7.1.10.

Prior to and after the primary analysis cut-off date (10-Aug-2018), in some circumstances patients may be allowed to continue to receive study treatment beyond disease progression as per RECIST 1.1 criteria (Section 6.1.5.1). These patients will continue assessments as outlined in Section 7, and will complete the EOT visit only after permanent discontinuation of study treatment.

[redacted]

Patients who discontinue treatment prior to the primary analysis cut-off date (10-Aug-2018) for reasons other than irRECIST PD will have tumor assessments per Table 7-1 until withdrawal of consent, death, lost to follow-up or eventual irRECIST PD per BIRC even if new post treatment ANP is started.

After the primary analysis cut-off date (10-Aug-2018), post-treatment efficacy follow-up will be discontinued. Therefore, for patients who discontinue study treatment for any reasons after the primary analysis cut-off date, post treatment efficacy follow-up will not be performed and these patients will enter the safety follow-up. If clinically indicated, patients may continue to undergo tumor response assessments during the safety follow-up according to local or institutional standard of care; however these tumor response assessments will no longer be reported in the eCRF.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.1.5.1 Replacement policy

Not applicable

7.1.6 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study anymore, and does not allow any further collection of personal data.

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

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

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

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

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.

[redacted]

7.1.7 Follow up for safety evaluations

All patients must be followed for safety 150 days after the last dose of PDR001 (Appendix 3).

After the 30-Day on-site safety follow-up visit, patients will be followed (via telephone call or on-site visit if patient happens to be visiting the site) at 60, 90, 120 and 150 days after the last dose of PDR001. However, women of childbearing potential must return to the site for the 150-Day safety follow-up visit, in order, to have a serum pregnancy test; for 60, 90, 120 days safety follow-up, women of childbearing potential will perform a urine pregnancy test at home.

All safety assessments should be completed as per Table 7-1. However, if the patient begins post treatment antineoplastic medication during the period between the 30-Day and 150-Day safety follow-up, the collection of new SAEs and AEs unrelated to study medication will stop, and thereafter only suspected AEs and suspected SAEs will continue to be collected up to 150-Day safety follow-up. Suspected SAEs will continue to be collected beyond the 150-Day safety follow-up. Data collected should be added to the appropriate eCRF pages.

There are no changes in safety evaluations after the primary analysis cut-off date.

7.1.8 Follow-up for efficacy evaluations

Patients who discontinue treatment for reasons other than irRECIST PD will have tumor assessments per Table 7-1 until withdrawal of consent, death, lost to follow-up or eventual irRECIST PD per BIRC even if new post treatment ANP is started.

After the primary analysis cut-off date (10-Aug-2018), post-treatment efficacy follow-up will be discontinued. Therefore, for patients who discontinue study treatment for any reasons after the primary analysis cut-off date, post treatment efficacy follow-up will not be performed and these patients will enter the safety follow-up. If clinically indicated, patients may continue to undergo tumor response assessments during the safety follow-up according to local or institutional standard of care; however, these tumor response assessments will no longer be reported in the eCRF.

7.1.9 Survival follow-up

Patients will enter the survival follow-up period once they complete the safety follow-up period or efficacy follow-up, whichever is last. Patients will then be contacted by telephone every 12 weeks to follow-up on their survival status. Any new antineoplastic medications that have been started since the last contact date will also be collected during these phone calls.

7.1.10 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" (three documented attempts) by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

[redacted]

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be assessed locally and centrally according to the Novartis guideline version 3.2 (Appendix 1) based on RECIST 1.1 (Eisenhauer et al 2009) and irRECIST (Appendix 2). The imaging assessment collection plan is presented in Table 7-2. Details of the central review process will be described in the independent review charter.

Imaging data will be centrally collected 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 as described in Section 7.2.4.

Information regarding prior interventions (e.g., radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening and prior interventions should be transmitted to the imaging CRO via the Baseline Clinical Form along with the screening images for review by the independent radiologist. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

Information regarding cytology results should be transmitted to the imaging CRO via the Cytology Form for all visits, when applicable, for review by the independent radiologist. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

After primary analysis cut-off date (10-Aug-2018), medical imaging data and information regarding cytology results will no longer be collected and transmitted to the imaging Contract Research Organization (CRO) for central tumor response evaluation. Tumor response will be assessed locally by investigator, according to RECIST 1.1 (Appendix 1) and irRECIST (Appendix 2).

[redacted]

Table 7-2 Imaging Assessment Collection Plan

Procedure	Screening (Day -28 to Day -1)	During Treatment/Follow-up (+/- 7 day window)
Chest, abdomen and pelvis CT or MRI (with contrast enhancement)	Mandated	**Before the primary analysis cut-off date (10-Aug-2018):** **Treatment Period:** Every 8 weeks counting from Cycle 1 Day 1 for the first 13 cycles and then every 12 weeks from Cycle 13 Day1 thereafter **EOT:** If a scan was not conducted within 30 days prior to end of study treatment. **Efficacy follow-up:** Continue same schedule as during treatment period until BIRC confirmed irRECIST progression **After the primary analysis cut-off date (10-Aug-2018):** **Treatment Period:** scheduled according to local or institutional standards of care and when clinically indicated, and continue until locally-determined disease progression (per RECIST 1.1 or irRECIST) **EOT:** No scan is needed at EOT visit. **Efficacy follow-up:** Post-treatment efficacy follow-up will no longer be performed.
Brain CT or MRI	Mandated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Whole body bone scan	If clinically indicated	If clinically indicated
Localized bone CT, MRI or X-ray	For any lesions identified on the "clinically indicated" baseline whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

7.2.2 Baseline imaging assessments

Imaging assessments will be performed at screening 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 baseline images for this study. Any imaging assessments obtained after start of study treatment cannot be considered baseline images.

The following assessments are required at screening:

- Computed Tomography (CT) with IV contrast or Magnetic Resonance Imaging (MRI) of Chest, abdomen and pelvis
  - The preferred radiologic technique is CT with intravenous (IV) contrast. If a patient is known to have a contraindication to CT contrast or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed
- Brain CT with IV contrast or MRI scan

[redacted]

  - If brain lesions are documented at baseline, scans need to be continued following the same schedule as CT/MRI of chest, abdomen and pelvis. The same methodology as used at screening should be used. Contrast enhanced brain MRI is preferred. However, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.
- A whole body bone scan according to institutional guidelines [e.g. Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride positron emission tomography (NaF PET)], if clinically indicated.
  - Whole body bone scans is not required for any timepoint, unless clinically indicated. It will not be the routinely used tumor imaging to monitor the response to the therapy.
- If skeletal lesions are documented on the whole body bone scan at baseline, localized bone CT, MRI or x-ray will be performed to follow up these lesions with the same schedule used for the tumor assessment by CT/MRI as described in Table 7-2.
- CT or MRI of other metastatic sites not captured by any of the above listed images (e.g., neck), if clinically indicated.
  - If additional sites of disease are documented at screening, scans need to be continued following the same schedule as CT/MRI of chest, abdomen and pelvis. The same methodology as at screening should be used.
- Chest x-rays and ultrasound must not be used to measure tumor lesions.

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.

7.2.3 Post-baseline imaging assessments

Imaging assessments as described in Table 7-2 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1).

Prior to the primary analysis cut-off date (10-Aug-2018), imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) until Cycle 13, and every 12 weeks (+/- 7 days) thereafter until disease progression per RECIST 1.1 or irRECIST per BIRC, death, lost to follow-up or withdrawal of consent. Imaging assessments should be scheduled using the date of first dose (Cycle 1 Day 1) as the reference date (not the date of the previous tumor assessment), and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

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 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

[redacted]

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 1.1 (Appendix 1) or per irRECIST (Appendix 2).

All study imaging (including any off-schedule imaging studies) should be submitted to the designated imaging CRO for quality control and central review.

After the primary analysis cut-off date (10-Aug-2018):

- For patients on study treatment, imaging assessments will be scheduled according to local or institutional standard of care, as clinically indicated, and will continue until study treatment discontinuation.
- **Imaging data will no longer be centrally collected and transmitted to the imaging CRO.** Tumor response will be assessed locally according to RECIST 1.1 (Appendix 1) and irRECIST (Appendix 2).
- 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 planned imaging assessment.

7.2.4 Timepoints at which progression is determined locally

All patients who have disease progression per RECIST 1.1 or disease progression per irRECIST 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. For expedited requests, the scans will undergo expedited central review (within 5 business days from the time of image receipt at the imaging CRO and once all applicable queries are resolved) and the results of the central review will be communicated to the site. While the investigator is waiting for the results from the central imaging CRO confirming disease progression, the patient should continue on study treatment. However, during this time, the investigator should do whatever is medically necessary for his/her patient.

If the central review determines disease progression as per RECIST 1.1 (and the patient does not meet the criteria in Section 6.1.5.1) or disease progression per irRECIST, then the patient will discontinue study treatment and subsequent tumor assessments are only required if the patient has not met the criteria for disease progression per irRECIST as per the central imaging vendor.

If the central review does not determine disease progression as per RECIST 1.1 or irRECIST, or the central reviewer determines disease progression as per RECIST 1.1, but the patient meets

[redacted]

the criteria in Section 6.1.5.1 to continue treatment, the patient should continue receiving the study treatment unless there is a medical need (i.e., rapid progression or clinical deterioration) for an immediate change in therapy. After the central reviewer determines disease progression per RECIST 1.1, an expedited review will be required only in case of disease progression determined locally per irRECIST at following assessments.

Patients will continue to have imaging performed as per protocol (Table 7-1) until the central review determines disease progression per irRECIST.

The imaging vendor will ensure that the central reviewers involved are blinded to the expedited status of the reading.

In summary, for expedited timepoints (assessed as PD by RECIST 1.1 or irRECIST by local):

Rapid image transmission to the central imaging CRO may be accomplished by uploading all digital images acquired by the Investigator in a secured website, while preserving the blinded status of the images.

- If central radiology determines PD as per RECIST 1.1, or PD per irRECIST , the study site will be informed. This patient should then discontinue study drug unless the criteria are met to continue study treatment beyond disease progression per RECIST 1.1 as described in Section 6.1.5.1. An expedited review at future assessments will only be required if PD per irRECIST is determined by the local investigator.
- If central radiology does not conclude PD as per RECIST 1.1 or PD as per irRECIST, the study site will be informed. As long as it is clinically acceptable, every effort should be made to continue the patient on study drug until PD as per irRECIST is determined by central review or for at least one subsequent radiological timepoint.

After the primary analysis cut-off date (10-Aug-2018):

- Imaging data will no longer be centrally collected and transmitted to the imaging CRO. Patients who have disease progression per RECIST 1.1 or irRECIST as determined locally do not require an expedited central review.
- Tumor response will be assessed locally (i.e. by investigator) according to RECIST 1.1 (Appendix 1) and irRECIST (Appendix 2).

7.2.5 Timepoints without locally determined progression

All imaging timepoints without locally determined progression per RECIST 1.1 or PD as per irRECIST will be read on an ongoing, non-expedited basis as detailed in the imaging manual to be provided by the designated imaging CRO and independent review charter. Results of these readings will not be communicated to the sites.

After the primary analysis cut-off date (10-Aug-2018), imaging data will no longer be centrally collected and transmitted to the imaging CRO.

7.2.6 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, weight, ECOG performance status, laboratory evaluations (including chemistry, hematology, hepatitis, coagulation, pregnancy, cytokines analysis), safety imaging (CT or MRI), and ECG as well as

collecting of the adverse events as well as collecting of the adverse events at every visit as indicated in Table 7-1. For details on AE collection and reporting, refer to Section 8.

7.2.6.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

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

7.2.6.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.

7.2.6.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.6.4 Performance status

ECOG Performance status scale will be used as described in the Table 7-1 and Table 7-3.

Table 7-3 ECOG performance status scale

Score	Performance 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 housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.2.6.5 Change in functional status of carcinoid syndrome

If a patient with non-functional tumor develops symptoms related to carcinoid syndrome (e.g. flushing, diarrhea) the change to "functional status" and the use of concomitant medications to control symptoms should be documented in the appropriate eCRF pages.

[redacted]

7.2.6.6 Laboratory evaluations

Table 7-4 Central Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting)
Coagulation	Screening: Prothrombin time (PT), International normalized ratio (INR]), Activated partial thromboplastin time (APTT) At all subsequent visits indicated in Table 7-1: APTT
Thyroid	At screening: TSH (Thyroid Stimulation Hormone), Free T3 and Free T4 At the subsequent visits as indicated in Table 7-1: TSH only. If TSH is abnormal, central lab will test Free T3 and Free T4
Hepatitis markers	HBV-DNA, HBsAg, HBsAb, HBcAb, HCV RNA-PCR
Cytokines	IFN-γ, IL-6, IL-1,TNF-α
Neuron specific enolase (NSE) level	NSE
Chromogranin A (CGA) level	CGA

Table 7-5 Local Clinical laboratory parameters collection plan

Test Category	Test Name
Urinalysis	Local Laboratory: Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If dipstick is abnormal then perform local laboratory Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Pregnancy Test	A serum pregnancy test must be performed at screening (at the local laboratory) within ≤ 72 hours before first dose of study treatment, at EOT, at 30-Day and 150-Day (for WOCBP) safety follow-up visits. A local laboratory urine pregnancy test must be performed at day 1 of every cycle beginning with Cycle 2, and at home every 30-Day after 30-Day safety follow-up visit until 120-Day follow-up.

All laboratory parameters assessed for safety purposes will be evaluated centrally except for urinalysis and urine/serum pregnancy tests that will be performed locally (Table 7-4 and Table 7-5). Samples for these parameters will be collected prior to the infusion of PDR001.

Local laboratory assessments may be performed if medically indicated or when the treating physician cannot wait for central laboratory results for decision making. In this particular situation, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

The results of the local laboratory will be recorded in the eCRF if the following criteria are met:

- A treatment decision was made based on the local results, or
- There are no concomitant central results available

However, only laboratory results from the central laboratory can be used to determine patient eligibility.

[redacted]

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the [Laboratory Manual].

7.2.6.6.1 Hematology

Hematology tests are to be performed at each scheduled visit as indicated in Table 7-1 and Table 7-4. Lab assessment done ≤ 4 days before first dose of study treatment are permitted to be used as Cycle 1 Day 1 labs and do not need to be repeated. Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other) will be measured.

7.2.6.6.2 Clinical chemistry

The clinical chemistry panel will be performed as per the assessment schedule in Table 7-1 and Table 7-4. Lab assessment done ≤ 4 days before first dose of study treatment are permitted to be used as Cycle 1 Day 1 labs and do not need to be repeated. Blood urea, creatinine, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, calcium, phosphorous, albumin, and uric acid Albumin, Alkaline phosphatase, ALT , AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting) will be measured.

7.2.6.6.3 Thyroid function

Thyroid function will be performed at:

- Screening: TSH, Free T3, Free T4
- Day 1of subsequent cycles, EoT, 30-Day safety follow-up: TSH
  - If TSH is abnormal, central lab will test Free T3 and Free T4.

7.2.6.6.4 Coagulation

Coagulation test will be performed as described in Table 7-1 and Table 7-4:

- At screening: Prothrombin time (PT), International normalized ratio (INR]), Activated partial thromboplastin time (APTT)
- At all subsequent visits: APTT

7.2.6.6.5 Cytokine analysis

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

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

[redacted]

Samples for cytokine panel at screening will be stored below -70°C.

7.2.6.6.6 Hepatitis marker

Hepatitis panels will be performed as per Table 7-4.

HBV-DNA serology (including HBV-DNA, HBsAg, HBsAb, HBcAb) and HCV RNA-PCR test will be performed at screening within 28 days prior to start of study treatment and as clinically indicated (hepatitis markers should be evaluated for precautionary safety monitoring of viral re-activation while on study treatment).

During the screening period, patients must be screened for HBV and HCV (current or past history of infection). Careful medical history must be taken for all patients to look for risk factors (family history of HBV and HCV, intravenous drug abuse, unprotected sex, dialysis, blood transfusions, etc.), and any past or present HBV symptoms (e.g., jaundice, dark urine, light colored stools, right upper quadrant pain).

Hepatitis B:

At screening, all patients will be tested for:

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

Hepatitis C:

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

After start of the study treatment and until 150-Day safety follow-up, testing for HBV and HCV should be performed if clinically indicated (for example: rule out viral causality in case of DILI).

7.2.6.6.7 CgA and NSE

The tumor markers, CgA and NSE, will be collected as described in Table 7-1.

7.2.6.6.8 Pregnancy and assessments of fertility

Serum and Urine pregnancy test will be performed as outlined in Table 7-5.

Women of child-bearing potential will have serum pregnancy tests within 72 hours prior to the first dose of study treatment. Monthly urine pregnancy tests will then be required to be performed on day 1 of every cycle beginning with Cycle 2, followed by serum pregnancy test at the End of Treatment visit, 30-Day and 150-Day Safety follow-up visit. During the follow-up period after the 30-Day Safety Follow-up visit through the 120-Day follow-up telephone call, women of child-bearing potential will perform at-home urine pregnancy testing every 30 days using kits provided. Women of child bearing potential must return to the site for the final pregnancy test (150-Day safety follow-up visit). For all pregnancy tests performed at home, the site personnel will follow-up with the patient via telephone call to collect the date and the test results and document the information in the patient's source documents. For the 30-Day and

150-Day safety follow-up visits, the results of the serum pregnancy test must be also documented in the patient's source documents and will be reported on the CRF.

Women of child-bearing potential will be instructed to contact the site immediately at any time during the study (on-treatment or during follow-up) should they have a positive pregnancy test.

7.2.6.7 Cardiac assessments

7.2.6.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as per Table 7-6.

Table 7-6 Local ECG collection plan

Cycle/weeks	Day	Time	ECG Type
Screening	Anytime	Anytime	12 Lead
Every 12 weeks starting from Cycle1 Day1,	1	Pre-dose	12 Lead
EOT	1	Anytime	12 Lead
Unscheduled ECG, if clinically indicated		Anytime	12 Lead

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.2.7 Pharmacokinetics and immunogenicity (IG) assessment

The exact date and clock times of drug administration PK and IG blood draw will be recorded on the appropriate eCRF.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein opposite to the arm used for infusion.

A total of 5 mL of blood will be collected for PDR001 PK and IG analysis in serum (2 mL for PDR001 PK and 3 mL for IG).

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 (Table 7-7). After clotting, the resulting serum will be separated in aliquots and will be stored frozen until analysis.

Refer to the [Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK and IG samples.

If patients experience a SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained as close as possible to the event occurrence. If patients experience suspected immunologically related AE such as infusion-related reaction, hypersensitivity, cytokine release syndrome and anaphylaxis, an unscheduled IG blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of PK blood draw should be recorded.

[redacted]

[redacted]

After the primary analysis cut-off date (10-Aug-2018), no additional PK and IG samples will be collected for the patients still ongoing on the study, unless requested by the Investigator.

Table 7-7 Pharmacokinetic and immunogenicity blood collection log

Cycle	Day	Scheduled timepoint (hours)	Dose reference ID	PK Sample number	IG Sample number
1	1	Predose/0hrs[a]	1	101	201
1	1	End-of-Infusion[b]	1	102	
2	1	Predose/0hrs	2	103	202
3	1	Predose/0hrs	3	104	203
3	1	End-of-Infusion[b]	3	105	
4	1	Predose/0hrs	4	106	204
5	1	Predose/0hrs	5	107	205
6	1	Predose/0hrs	6	108	206
7	1	Predose/0hrs	7	109	207
8	1	Predose/0hrs	8	110	208
9	1	Predose/0hrs	9	111	209
10	1	Predose/0hrs	10	112	210
11	1	Predose/0hrs	11	113	211
12	1	Predose/0hrs	12	114	212
13	1	Predose/0hrs	13	115	213
19	1	Predose/0hrs	14	116	214
25[c]	1	Predose/0hrs	15	117	215
EoT	N/A	Anytime	N/A	118	216
30-Day Safety F/U visit	N/A	Anytime	N/A	119	217
150-Day Safety F/U visit (for women of childbearing potential)	N/A	Anytime	N/A	120	218
● Unscheduled[d] ● Unscheduled at the time of PD based on RECIST 1.1[e] ● Unscheduled at the time of PD based on irRECIST[e] ● Unscheduled at the time of suspected irAE (only IG sample)	N/A	Anytime	N/A	1001+	2001+

[a]All predose samples must be collected immediately prior to starting the infusion (day of infusion)

[b]End-of-infusion samples should be collected within 30 minutes post-infusion.

[c]PK and immunogenicity samples will not be collected after cycle 25 even if the patient continues treatment beyond cycle 25.

[d]Unscheduled PK and immunogenicity samples may be collected at any time if clinically indicated or at the Investigator's discretion and must be sequentially numbered as 1001, 1002, 1003, etc. for PK samples, and 2001, 2002, 2003, etc. for immunogenicity samples.

[e]An unscheduled PK sample and an unscheduled immunogenicity sample should be collected upon confirmed disease progression based on RECIST 1.1 and irRECIST.
Immunogenicity samples are collected together with PK samples. **After the primary CSR data cut-off date no additional PK and IG samples will be collected for the patients still ongoing on the study, unless requested by the**

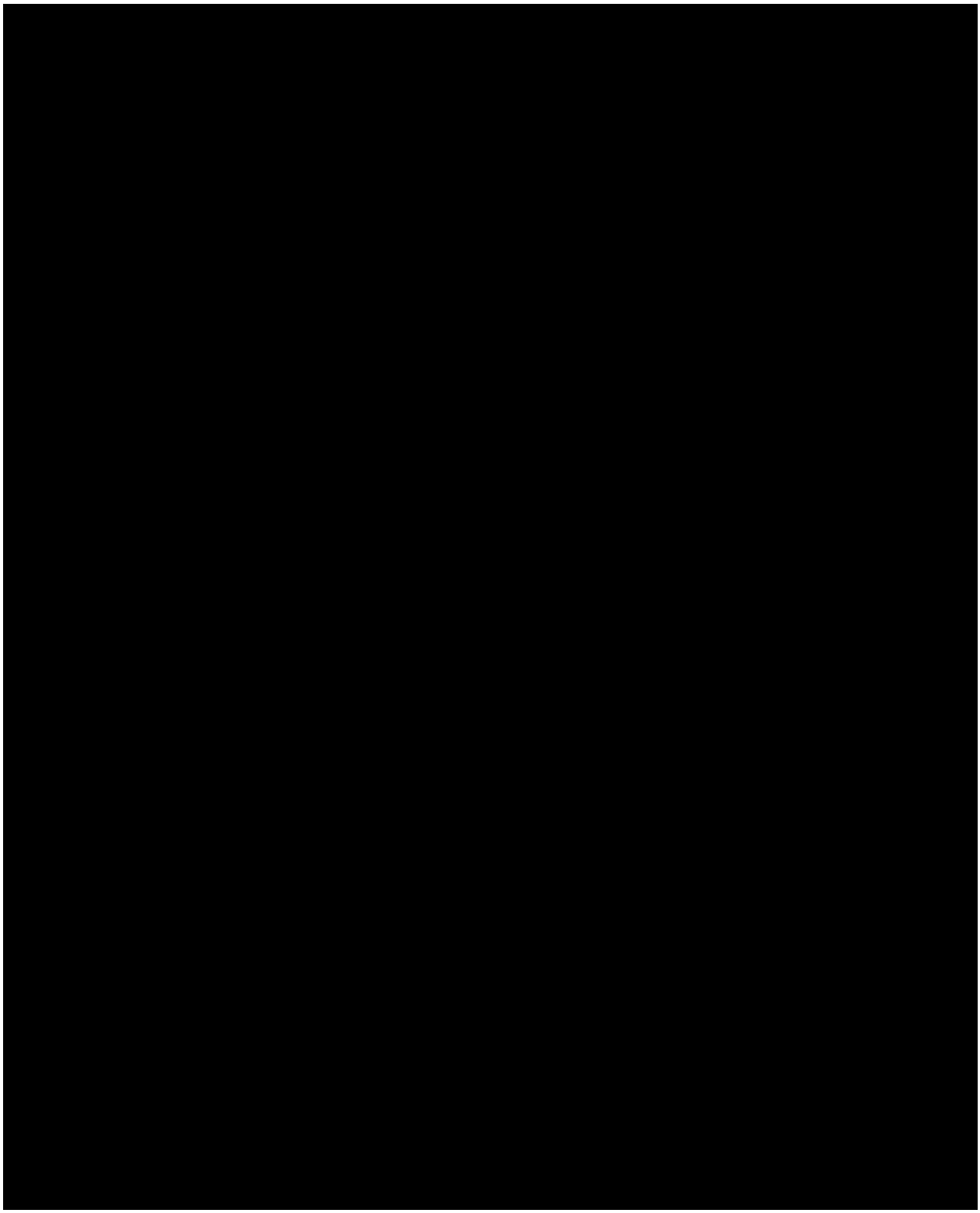
[redacted]

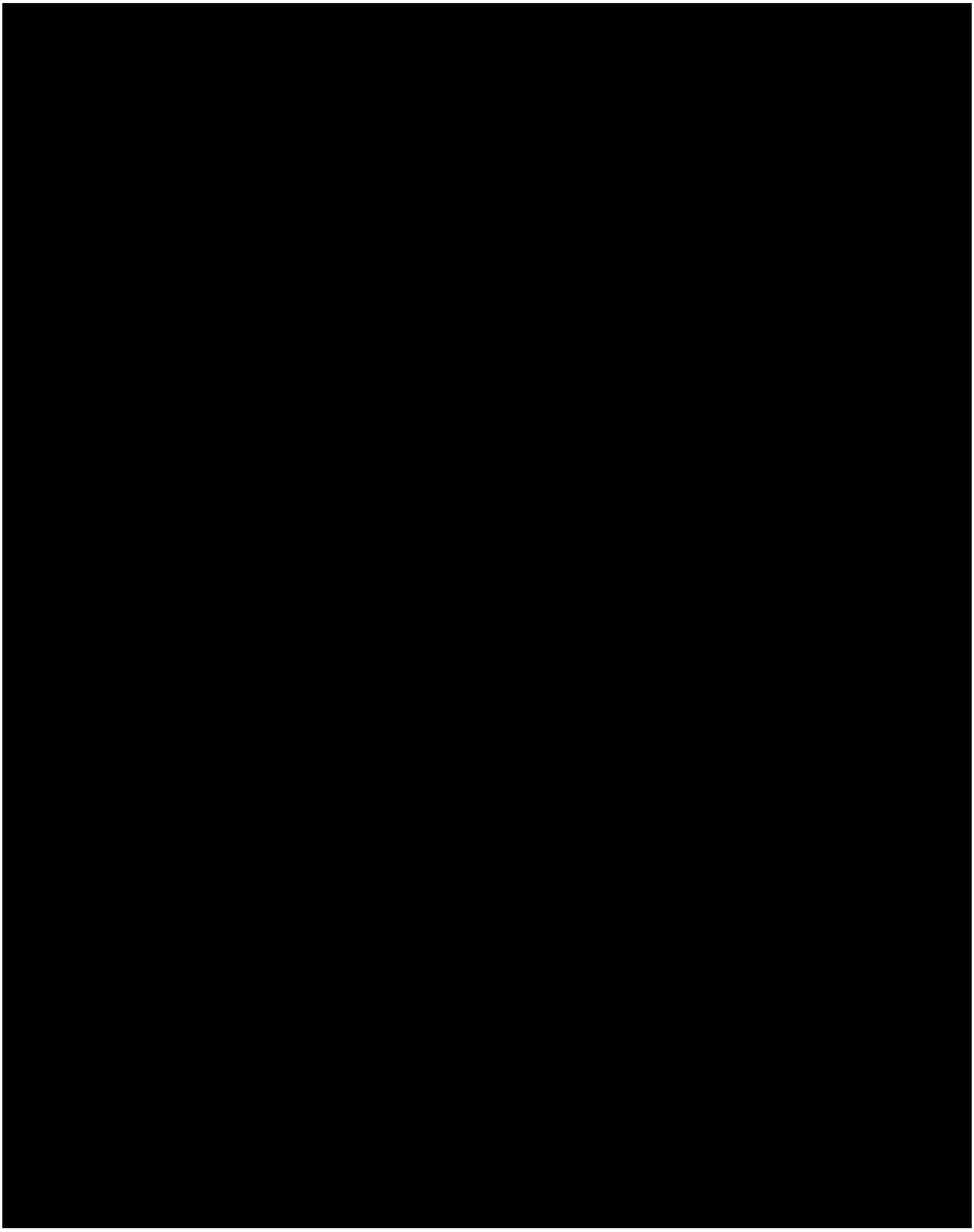
Cycle	Day	Scheduled timepoint (hours)	Dose reference ID	PK Sample number	IG Sample number
Investigator. Blood samples are collected from the arm opposite from infusion site.					

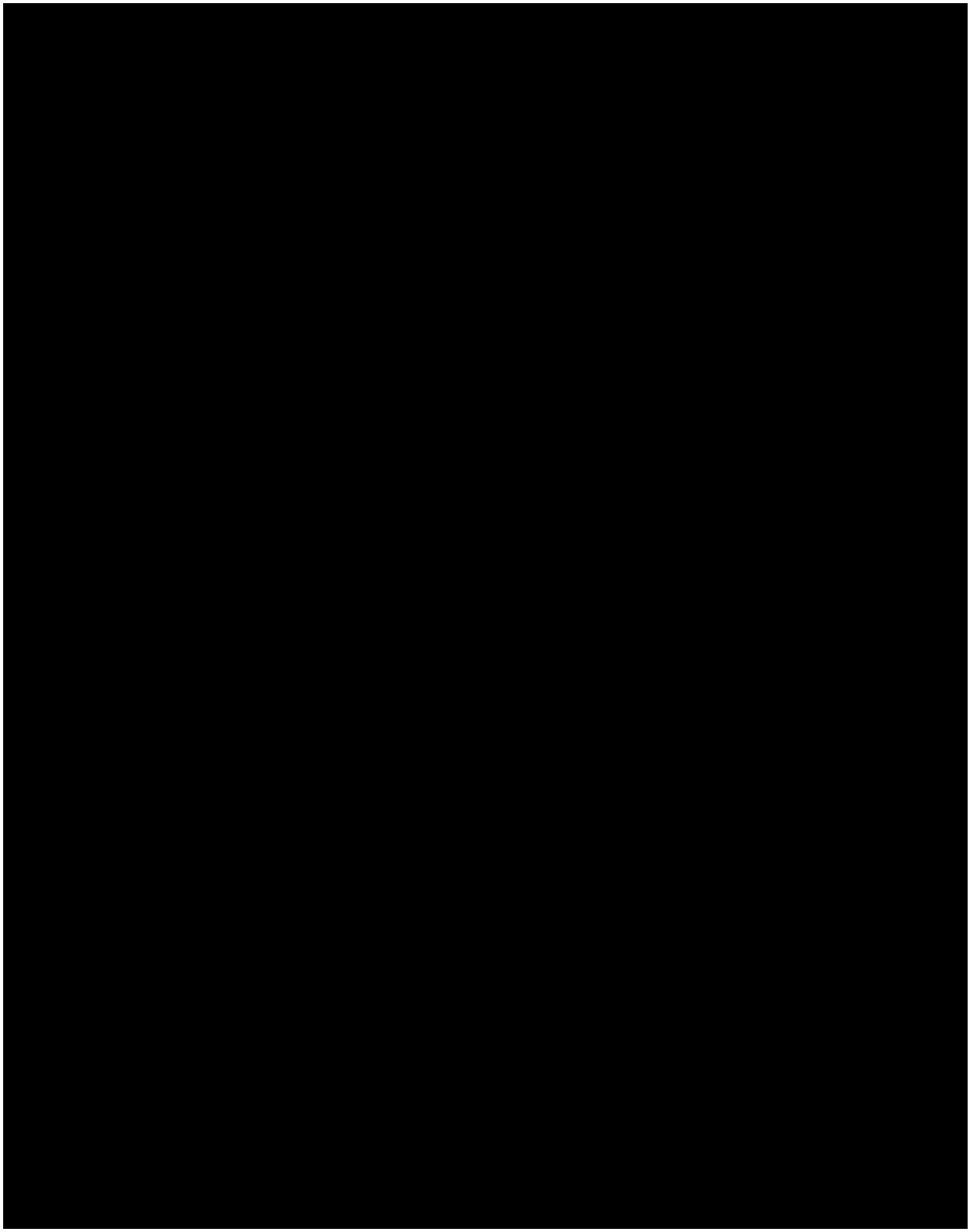
7.2.7.1 Analytical method

Bioanalysis for pharmacokinetic and IG assessment will employ the validated assays:

- The assay to quantify PDR001 will be a validated LCMS. The details of the assay will be documented in the [Bioanalytical Report].
- The assay to quantify and assess the IG will be a validated three-tier ELISA assays (screening, confirmatory and titer assays). The details of the assay will be documented in the [Bioanalytical Report].







7.2.9 Resource utilization

Not applicable

7.2.10 Patient reported outcomes

The European Organisation for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30, version 3.0) and the EuroQoL 5-level instrument (EQ-5D-5L, tablet version) will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms, treatment-related side effects, and global health status. The EORTC QLQ-C30 and EQ-5D-5L are recognized reliable and valid measures (Aaronson 1993, Rabin 2001) frequently used in clinical trials of patients with advanced or metastatic cancer.

All patient-reported outcome (PRO) measures (e.g, EORTC QLQ-C30, EQ-5D-5L) will be administered before any study drug administrations at the visits indicated in Table 7-1 and Table 7-9. Collections of PRO measures have a ±7 day window unless otherwise indicated.

All PRO data will be collected using an electronic tablet device and should be administered in the patient's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the patient's perspective. Patients should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all patients, including data from the efficacy follow-up however, if patients refuse to complete questionnaires, this should be documented in study source records. Patient's refusal to complete study questionnaires are not protocol deviations.

Completed questionnaires, including both responses to the questions and any unsolicited comments provided by the patient, must be reviewed and assessed by the investigator before

the clinical examination for responses which may indicate potential AEs or SAEs. This review should be documented in study source records.

If an AE or SAE is confirmed then the physician should record the event as instructed in Section 8 of this protocol. Investigators should not encourage the patients to change responses reported in questionnaires.

After the primary analysis cut-off date (10-Aug-2018), patient-reported outcome questionnaires (EORTC QLQ-C30, EQ-5D-5L) will no longer be collected.

Table 7-9 PRO questionnaires

Patient Questionnaires	Study Period	Visit	Time point
EORTC QLQ-C30 and EQ-5D-5L	Screening	Day -28 to Day -1	Prior to any clinical assessments, drug dosing or diagnostic testing
	Treatment*	Every 8 weeks from Cycle 3 Day 1 for the first 13 cycles and every 12 weeks from Cycle 13 Day1 thereafter	
	End of treatment*	EOT visit	
	Safety Follow-up*	30-Day Safety Follow-up visit	
	Efficacy follow-up*	Continue same schedule as during treatment period until BIRC confirmed irRECIST progression	
*After the primary analysis cut-off date (10-Aug-2018), patient-reported outcome questionnaires (EORTC QLQ-C30, EQ-5D-5L) will no longer be collected.			

7.2.10.1 EORTC QLQ-C30

The EORTC QLQ-C30 contains 30 items and is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale (Aaronson et al 1993).

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. All scoring will follow the scoring procedures defined by the EORTC Scoring Manual (Fayers et al 2001).

7.2.10.2 EQ-5D-5L

The EQ-5D-5L (tablet version) is a standardized measure of health utility that provides a single index value for one's health status. The EQ-5D-5L is frequently used for economic evaluations of health care and has been shown to be a valid and reliable instrument (The EuroQol Group 1990, Rabin 2001). The EQ-5D-5L contains one item for each of five dimensions of HRQOL (i.e., mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). Response options for each item vary from having no problems (e.g., "…no problems walking about"), moderate problems (e.g., "…some problems walking about"), or extreme problems (e.g., "…unable to walk about"). Patient responses to the five dimensions of HRQOL reflect a specific health state that corresponds to a population preference weight for that state on a continuous scale of 0 (death) to 1 (perfect health). A visual analog scale (ranging from 0 to 100)

[redacted]

is also included to capture patient's rating of their overall health status. Higher scores of the EQ-5D-5L represent better health states. All scoring and handling of data will follow the User's Guide defined by the EuroQoL Group (van Reenen and Janssen 2015).

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.

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least:

- 150 days following the last dose of PDR001 OR
- Until the start of a new post treatment antineoplastic medication if administered during the period between the 30-Day safety follow up and 150-Day safety follow-up. If a patient starts a post treatment antineoplastic therapy after the 30-Day safety follow-up, then only adverse events suspected to be related to study treatment should be collected out to 150 days after discontinuation of PDR001.

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 and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (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 (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 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
4. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
5. 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

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

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

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

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

[redacted]

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.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. The following AESIs are discussed in detail in the latest [Investigator Brochure]:

- Endocrinopathies (Hypothyroidism, hyperthyroidism, diabetes, hypophysitis and hypopituitarism)
- Pneumonitis
- Diarrhea/colitis
- Hepatitis
- Nephritis
- Encephalitis
- Skin/rash

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

[redacted]

  - 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

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent must be reported to Novartis within 24 hours of learning of its occurrence and until:

- Suspected SAEs up to 150-Day safety follow-up and beyond
- Non-suspected SAEs up to 150-Day safety follow-up or start of new post treatment anti-neoplastic medication if administered during the period between the 30-Day safety follow-up and 150-Day safety follow-up, whichever is sooner (see Appendix 3)

If a patient starts a post treatment antineoplastic therapy after the 30-Day safety follow-up, then only SAEs suspected to be related to study treatment should be collected out to 150 days after discontinuation of PDR001. SAEs suspected to be related to PDR001 will continue to be collected beyond the 150-Day safety follow-up visit.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes 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.

Any SAEs experienced after the reporting period described above should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with

[redacted]

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 Emergency unblinding of treatment assignment

Not applicable

8.4 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.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment 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.

8.5 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.

8.6 Data Monitoring Committee

Not applicable

8.7 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial.

The SC will ensure management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. The SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study patient 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 subject 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 CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

[redacted]

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

9.3 Data collection

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 and 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.

[redacted] PK sampling, Laboratory samples for hematology, chemistry, coagulation (analyzed by central laboratory), Imaging, patient questionnaires (ePRO), will be collected at investigator sites.

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. The site staff designated by the investigator will enter the information required by the protocol onto the eCRFs as well as onto the designated CRO's requisition form. One copy of the requisition form will be forwarded to the central lab along with the corresponding samples with required information (including study number, subject ID) and one copy will be retain by the site.

Patient questionnaires data will be entered into an electronic PRO by the patient. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel 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.

[redacted]

10 Statistical methods and data analysis

Cut-off date for the primary safety and efficacy analysis will be 1 year after Last Patient First Treatment (LPFT) in the initially enrolled well-differentiated NET group. This analysis will include data from patients with well-differentiated NET and poorly-differentiated GEP-NEC groups. It is expected that at the time of this analysis all patients from the original poorly-differentiated GEP-NEC group will have at least 11 months follow-up. This analysis will be summarized in a CSR.

The additional data for any patients continuing to be followed up past this time, as allowed by the protocol, will be further summarized in a final study report after all patients discontinued treatment and completed the safety follow-up.

All analyses will be performed separately for the two groups of well-differentiated NET and poorly-differentiated GEP-NEC unless otherwise specified. Patients will be analyzed according to the group they were assigned at baseline.

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.

Except if otherwise specified, categorical data will be presented as contingency tables (frequencies and percentages). For continuous data summary statistics of 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 will not be included in analyses, but will be reported in the clinical study report (CSR) as separate listings.

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 and who received one dose of any study treatment (i.e. at least one dose of PDR001 (including incomplete infusion)).

10.1.2 Safety set

The Safety Set is defined in the same way as the FAS and includes all patients who received at least one dose of study treatment (i.e. at least one dose of the PDR001 (including incomplete infusion)).

10.1.3 Per-Protocol set

Not applicable.

10.1.4 Dose-determining analysis set

Not applicable.

[redacted]

10.1.5 Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PAS) includes all patients who provide at least one evaluable PDR001 PK concentration. For a concentration to be evaluable, patients are required to:

- receive one of the planned treatments of PDR001 prior to sampling
- for pre-dose samples, have the sample collected before the next dose administration
- for end-of-infusion samples, have the sample collected within 2 hours post end of infusion

10.1.6 Other analysis sets

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for all patients for the FAS.

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

Relevant medical histories and current medical at baseline will be summarized by system organ class and preferred term for all patients.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in weeks to PDR001 as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the Safety set.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized for all patients and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system for all patients.

10.4 Primary objective

The primary objective is to estimate the antitumor activity of PDR001 as a single agent in well-differentiated NET and poorly-differentiated GEP-NEC groups.

[redacted]

10.4.1 Variable

The primary efficacy variable of the study is overall response rate (ORR), defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR), as per blinded independent review committee. ORR will be evaluated according to RECIST 1.1 (see Appendix 1 for details).

ORR will be calculated within each group based on the FAS and according to the ITT principle.

10.4.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis testing will be conducted. The objective of the study is to demonstrate the antitumor activity of PDR001 as measured by ORR.

The response rate within each group on the FAS population with 95% two-sided confidence interval (exact method) will be computed.

Group 1: Well-differentiated NET

The results in this group will be considered a success if both of the following conditions are met:

1. a clinically relevant response rate of at least 10% is observed
2. 95% two-sided CI for ORR excludes the value 3%.

With 90 treated patients enrolled, the success corresponds to at least 9 responders observed (i.e. a response rate of 10% with [4.7; 18.1] 95% CI).

In the absence of historical comparator in this setting, response rates reported in placebo arms of previous randomized phase III studies in earlier lines of treatment can be considered as a valid historical reference for ORR in well-differentiated NET (Table 1-1). A 95% two-sided CI excluding the value 3% will ensure that the clinically relevant observed response rate is significantly higher than expected placebo response rate.

Group 2: Poorly-differentiated GEP-NEC

This group will enroll approximately 20 patients. Estimates of the ORR along with 95% two-sided CI will be presented. Additionally, the interval probabilities for the true ORR lying within the intervals stated below will be computed.

- 0 - <3% unacceptable efficacy
- 3% - <10% limited efficacy
- 10% - <20% moderate efficacy
- ≥20% clinically relevant efficacy

For this analysis a prior distribution for the parameter of interest, ORR, must be specified. For the current study, the prior clinical assumption for PDR001 in the selected patient population is used in order to derive a minimally informative unimodal Beta prior distribution that reflects the level of uncertainty around ORR before starting the current trial (Neuenschwander et al 2008). The prior mean ORR is set to be equal to 15% and the parameters of the minimally informative Beta prior distribution of ORR have been set up as follows:

- $a/(a+b) = 0.15$

[redacted]

- a = 0.176
- b = 1.0

At the primary analysis, this prior distribution will be updated with observed ORR data and probabilities that the true ORR lies within the above intervals will be reported.

10.4.3 Handling of missing values/censoring/discontinuations

For the computation of ORR, all confirmed responses (CR or PR) reported up to the analysis cut-off will be included. Patients with no valid radiological assessment or unconfirmed responses will be considered as non-responders. In particular, patients with CR or PR at the last radiological assessment prior to cut-off and no response at the previous assessment are by definition unconfirmed and will be considered as non-responders for the primary analysis.

10.4.4 Supportive and Sensitivity analyses

A sensitivity analysis considering patients with unconfirmed PR or CR (i.e. with PR or CR at the last assessment prior to the cutoff and ongoing in efficacy follow-up) as responders may be performed.

Primary and sensitivity analyses will be repeated using overall response based on local review.

10.5 Secondary objectives

The key secondary objective in this study is to estimate efficacy of PDR001 in each group using the duration of response per RECIST 1.1 and based on tumor response data per BIRC. Furthermore, tumor related endpoints such as disease control rate (DCR), time to response (TTR) and PFS will be evaluated based on RECIST 1.1 and irRECIST. Additional secondary endpoints include overall survival rate at 1 and 2 years, HRQoL, CgA and NSE, PK and safety.

Antitumor activity (assessed by ORR and DoR per RECIST 1.1 and BIRC) in each of the three well-differentiated NET cohorts (pancreatic, GI, thoracic) will also be evaluated as secondary endpoint. If heterogeneity in ORR is observed among the three cohorts, a probabilistic evaluation, using simulations or any other appropriate method, will be conducted in order to assess observed difference. Details will be provided in the statistical analysis plan (SAP).

10.5.1 Key secondary objective(s)

Duration of Response (DoR)

Duration of response (DOR) only applies to patients whose best overall response is complete response (CR) or partial response (PR) based on tumor response data per blinded independent central review. DOR will be evaluated according to RECIST 1.1 (see Appendix 1 for details).

The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer. Patients continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment. DOR based on RECIST 1.1 will be listed and summarized for all patients in the FAS with confirmed BOR of CR or PR.

[redacted]

10.5.2 Other secondary efficacy objectives

All secondary efficacy endpoints according to RECIST 1.1 or irRECIST will be based on tumor assessments as per BIRC. The local radiology assessments will be used as supportive analysis.

10.5.2.1 Efficacy endpoints according to RECIST 1.1

Disease control rate (DCR)

DCR is defined as the proportion of patients with best overall response of CR, PR or SD according to RECIST 1.1 criteria and as per central review (see Appendix 1 for details).

DCR will be calculated based on the FAS. DCR and its 95% confidence interval will be presented for all patients.

Time to response (TTR)

Time to response (TTR) is defined as the time from the date of start of treatment to the first documented response of either complete response (CR) or partial response (PR), which must be subsequently confirmed (although date of initial response is used, not date of confirmation). TTR will be evaluated according to RECIST 1.1 (see Appendix 1 for details).

All patients in the FAS will be included in TTR calculations. Patients without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e., Last Patient Last Visit (LPLV)-First Patient First Visit (FPFV)) for patients with a PFS event (i.e., disease progression or death due to any cause), or at the date of the last adequate tumor assessment for patients without a PFS event. TTR will be listed and summarized for all patients. The distribution of time to response will be estimated using the Kaplan-Meier method only if a sufficient number of responses is observed.

Progression-free survival (PFS)

PFS is defined as the time from the date of first dose to the date of the first documented radiological progression or death due to any cause. PFS will be assessed via central review according to RECIST 1.1 (see Appendix 1 for further details). PFS will be censored if no PFS event is observed before the analysis cut-off date. The censoring date will be the date of the last adequate tumor assessment prior to cut-off.

PFS based on RECIST 1.1 will be analyzed in the FAS population. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for all patients.

10.5.2.2 Efficacy endpoints according to irRECIST

The definitions of the endpoints based on irRECIST are similar to those based on RECIST 1.1 and are provided in the Appendix 2. The following endpoints will be analyzed in the same way as described above for the endpoints based on RECIST:

- irORR
- irDoR
- irTTR

[redacted]

- irDCR
- irPFS.

10.5.2.3 Overall survival rate at 1 year and 2 years

OS is defined as the time from date of start of treatment to date of death due to any cause. If a patient is not known to have died, then OS will be censored at the latest date the patient was known to be alive (on or before the cut-off date). The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves.

Survival estimates at 1 year and at 2 years will be computed with 95% confidence interval.

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 separately for the well-differentiated NET and the poorly-differentiated GEP-NEC groups. In addition, pooled safety analyses based on all patients will be produced.

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 PDR001
3. Post-treatment period: starting at day 31 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. Additional summaries will be displayed to report deaths, all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to **150** days after last administration of PDR001.

The incidence of treatment-emergent adverse events (new or worsening from 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.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those starting during the post-treatment period will be flagged.

Project-specific AESIs should be defined in the case retrieval strategy (CRS) with regular updates whenever necessary, see also Section 8.1.3.

[redacted]

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be applicable.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following listings/summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v4.03

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.03,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the statistical analysis plan (SAP).

10.5.3.4 Other safety data

ECG

- 12-lead ECGs including PR, QRS, QT, QTcF intervals and heart rate (HR) will be obtained for each patient during the study. ECG data will be read and interpreted locally.
- Categorical Analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced.

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

[redacted]

10.5.3.5 Supportive analyses for secondary objectives

Efficacy analyses as per local review

The analyses based on the efficacy endpoints according to RECIST 1.1 and irRECIST (described in Section 10.5.2.1 and Section 10.5.2.2) will be repeated using local radiology review.

10.5.3.6 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed and summarized (see Section 10.3).

10.5.4 Pharmacokinetics

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) for PDR001 concentrations will be presented at each scheduled timepoint. For PDR001, pre-dose concentrations collected before dose administration on Day 1 of Cycle 2+ are Ctrough.

All concentration data for PDR001 will be displayed graphically.

10.5.4.1 Data handling principles

Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

Below the limit of quantitation (BLQ) values will be set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. BLQ values will be treated as missing for the calculation of the geometric means and geometric CV%.

10.5.4.2 Population pharmacokinetic analysis

If data permit, a mixed-effects model may be applied to the serum PDR001 concentration-time data to generate post hoc estimates of pharmacokinetic parameters using NONMEM to characterize PDR001 exposure. If there are sufficient data for analysis, the details of the population pharmacokinetic analyses will be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report. Data from this and other studies may be pooled for analysis.

10.5.5 Immunogenicity

Immunogenicity will be characterized descriptively by tabulating anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment.

10.5.6 CgA and NSE

The biochemical response will be assessed using the change from baseline for CgA and NSE levels.

[redacted]

Change from baseline in CgA and NSE will be summarized using descriptive statistics for all patients. CgA and NSE values might be analyzed on the logarithmic scale if their observed distribution is found be right skewed. [redacted]

10.5.6.1 Data handling principles

The lower limit of quantification (LLOQ) values for CgA and NSE will be specified by the laboratory running the assay.

Measures below the LLOQ will be handled as follows:

- If the proportion of measures below LLOQ is below 15%, all values specified as below LLOQ will be imputed by half of the LLOQ and the standard set of summary statistics will be used.
- If the proportion of measures below LLOQ is above 15%, but below 50%, an alternative choice of summary statistics requiring no imputation such as percentiles may be used.
- Otherwise the data will be missing
- When both baseline and post baseline values are below LLOQ, change from baseline will not be imputed and reported as missing.

Values below LLOQ will be shown as such in listings. All available data points obtained at scheduled and unscheduled visits will be considered for the analysis.

10.5.7 Resource utilization

Not applicable

10.5.8 Patient-reported outcomes

The EORTC QLQ-C30 questionnaire and the EQ-5D-5L will be used to collect patient's QoL data. The global health status/QoL scale score of the QLQ-C30 and the health status index score of the EQ-5D-5L are identified as the primary patient-reported outcome variables of interest. Physical functioning, emotional functioning and social functioning scale scores of the QLQ-C30, and overall health status of the EQ-5D-5L are identified as secondary patient-reported QoL variables of interest.

Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide for each respective patient questionnaire (Fayers 2001; van Reenen and Janssen 2015). No imputation procedures will be applied for missing items or missing assessments. Five health states from the EQ-5D-5L will be converted to index values during the data analysis stage and will be further defined in the analysis plan. In addition, the visual analog scale (ranging from 0 to 100) from the EQ-5D-5L will be evaluated for patient's rating of their overall health status.

The number of patients completing each questionnaire and the number of missing or incomplete assessments will be summarized for each scheduled assessment time points.

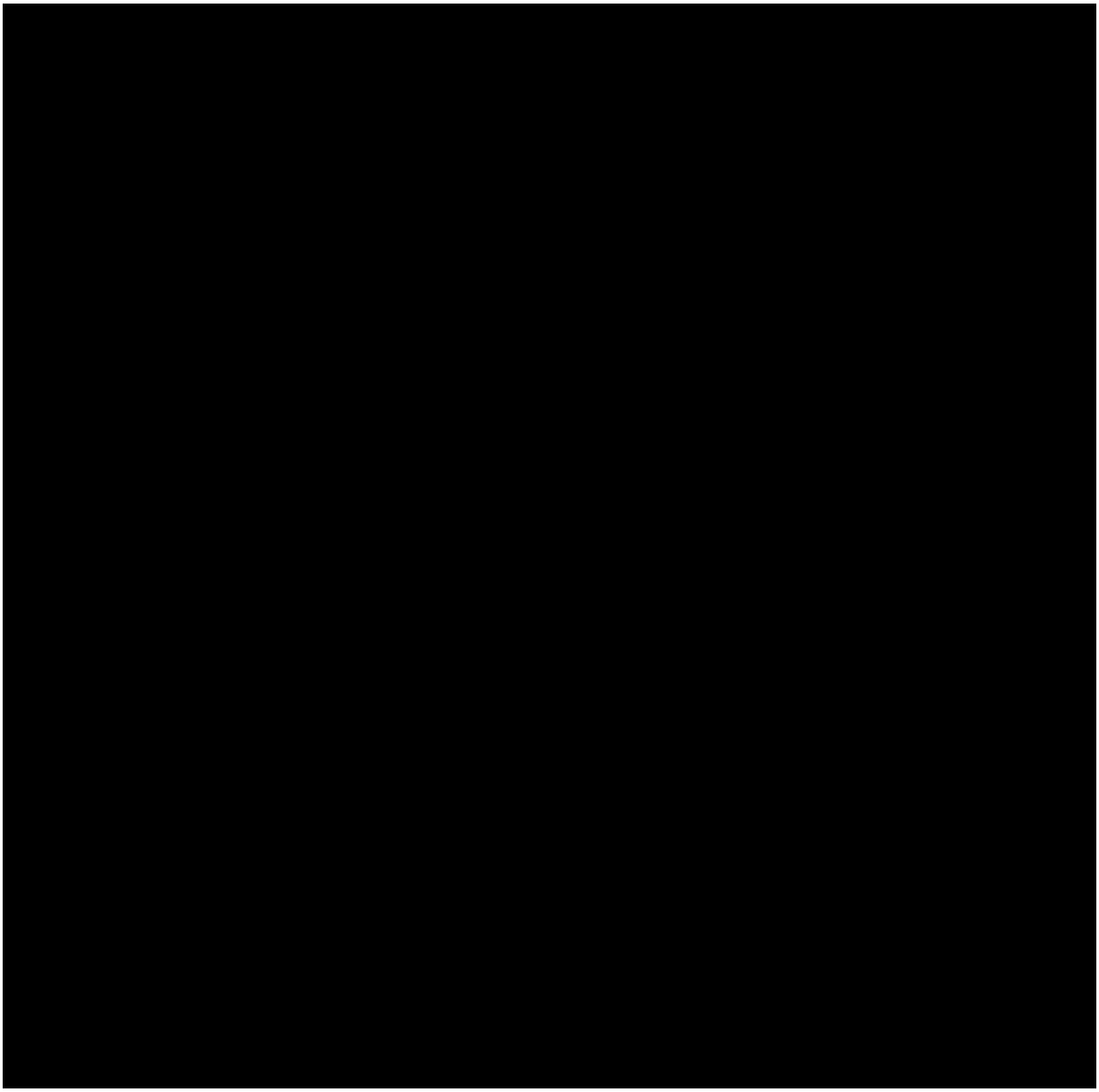
The FAS will be used for analyzing PRO data. No formal statistical tests will be performed. For the main analysis, patients with baseline and at least one non-missing post-baseline assessment

[redacted]

will be included. All available data until the end of treatment will be used in the repeated measures models for longitudinal data to assess the treatment effect over time.

A time-to-event approach may be considered as the secondary analysis, in which patients with no events will be censored at the latest available non-missing timepoint until end of treatment. Details will be specified in the SAP.

Descriptive statistics will be used to summarize the PRO scores and change from baseline in scales of the EORTC QLQ-C30 and health states, overall health status, and index values of the EQ-5D-5L at each scheduled assessment time point.



10.7 Interim analysis

An interim analysis for preliminary assessment of PDR001 in this patient population will be conducted once at least 30 patients from the well-differentiated NET group have 3 radiological assessments (week 24) or have discontinued study for any other reason. All available efficacy and safety data from the well-differentiated NET and poorly-differentiated GEP-NEC groups up to the cut-off date will be used for IA and reviewed by the Steering Committee. It is expected that at the time of the interim analysis all patients from the poorly-differentiated GEP-NEC group have at least undergone 2 radiological assessments. The study will not be stopped at the interim analysis for efficacy reasons regardless of efficacy results and will continue until mature data for all patients become available. If the study is stopped for safety reasons, the treatment continuation of patients who are deriving benefit from PDR001 treatment will be assessed on a case-by-case basis in consultation with the sponsor.

10.8 Sample size calculation

Group 1: Well-differentiated NET

In the absence of an established control treatment, ORR reported in the placebo arms of studies reported in Table 1-1 can serve as a reference in the well-differentiated NET group. A 3% ORR is therefore considered as a reasonable reference while an improvement up to 10% is considered as clinically meaningful in this patient population.

Total sample size of 90 patients was chosen such that with an observed 10% response rate, the corresponding 95% CI excludes the value 3%.

Approximately thirty patients will be recruited in each cohort NET cohort: pancreatic, GI and thoracic.

Operating characteristics in the well-differentiated NET group are given in Table 10-1. A sample size of 90 patients ensures a 90% probability of success if the true ORR is 15%.

Table 10-1 Operating characteristics for the full population of well-differentiated NET group

True response rate	Probability of observing 10% or more responders at the end of the study
10%	0.55
11%	0.67
12%	0.77
13%	0.84
14%	0.90
15%	0.94

In addition, Table 10-2 shows the probability of observing at least 3 responders in a cohort with 30 patients under the assumption of true response rate of 10-20% in this cohort.

Table 10-2 Probability of observing at least 3 responders in a cohort with more than 10% true response rate

True response rate in a cohort	Probability of observing 3 or more responders in a cohort with 30 patients at the end of the study
10%	0.59
12%	0.72
14%	0.81
16%	0.88
18%	0.93
20%	0.96

Group 2: Poorly-differentiated GEP-NEC

Approximately 20 patients will be enrolled in the poorly-differentiated GEP-NEC group. The operating characteristics are shown in Table 10-3 and Table 10-4. With the planned sample size the probability to observe at least moderate efficacy (≥10% ORR) is more than 80% if the true ORR is 15%. Posterior probability of a true ORR of at least moderate efficacy was computed for different scenarios assuming a minimally informative prior with Beta distribution and the

following parameters: a=0.176, b=1. Posterior probability of a true ORR to be ≥10% ORR is more than 70% if 3 responders are observed in 20 patients.

Table 10-3 Operating characteristics for the poorly-differentiated GEP-NEC group

True response rate	Probability of observing 2 or more responders (≥10% ORR) in 20 patients	Probability of observing 3 or more responders (≥15% ORR) in 20 patients
10%	0.61	0.32
12%	0.71	0.44
15%	0.82	0.60
18%	0.90	0.73
20%	0.93	0.79

Table 10-4 Posterior probability of a true ORR in the poorly-differentiated GEP-NEC group corresponding to at least moderate efficacy (>/=10% ORR)

Number of observed responders in 20 patients	Posterior probability for a true ORR ≥10%
1	15.8%
2	44.0%
3	71.4%
4	88.6%

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.

[redacted]

11.3 Informed consent procedures

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

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

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

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

[redacted]

11.4 Discontinuation of the study

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

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).

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

[redacted]

present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

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

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

11.6 Study documentation, record keeping and retention of documents

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

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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 study case report form (CRF) 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 CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless sponsor provides written

permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

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

14.1 Appendix 1: RECIST 1.1 Novartis guideline version 3.2

1 Introduction

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

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

2 Efficacy assessments

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

2.1 Definitions

2.1.1 Disease measurability

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

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

For patients without measurable disease see Section 3.2.8

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by CT/MRI can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.

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- 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.

2.1.2 Eligibility based on measurable disease

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

2.2 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan

slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

- 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 major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. 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 new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
  - 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.
  - Physical exams: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
  - Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
  - Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that

may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

2.3 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

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

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

[redacted]

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

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 2-1) and non-target lesions (Table 2-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 2-3) as well as the presence or absence of new lesions.

2.4.1 Follow-up and recording of lesions

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

2.4.1.1 Non-nodal lesions

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

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

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

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

2.4.1.2 Nodal lesions

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

[redacted]

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.

2.4.2 Determination of target lesion response

Table 2-1 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. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 2.2).

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 2-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target

[redacted]

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

[redacted]

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.

- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

2.4.3 Determination of non-target lesion response

Table 2-2 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[2].

1. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail..
2. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- 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 there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- 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

[redacted]

of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

2.4.4 New lesions

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

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

2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 2-3.

[redacted]

Table 2-3 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 2.4.

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

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.

3 Efficacy definitions

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

3.1 Best overall response

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

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

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

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

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

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

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

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

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

[redacted]

disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

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

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

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

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

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

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

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. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a best overall response of CR or PR , or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

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.

[redacted]

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

3.2 Time to event variables

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.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

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.

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.

[redacted]

3.2.4 PFS2

A recent EMA guidance (EMA 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues w.r.t. censoring foreseen.

3.2.5 Time to treatment failure

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

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

3.2.6 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).

[redacted]

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates... If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

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

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

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

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

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

3.2.7 Time to response

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

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

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to

[redacted]

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.

3.2.8 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.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

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

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

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

End dates

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

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

[redacted]

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.

3.2.9 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 non-measurable disease is derived slightly differently according to Table 3-1.

Table 3-1 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 2.4.

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

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

[redacted]

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

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

3.2.10 Sensitivity analyses

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

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

Table 3-2 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) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event

[redacted]

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1. =Definitions can be found in Section 3.2.7.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 3.2.7.
3. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example,

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palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

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 3-2 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

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

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

4 Data handling and programming rules

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

4.1 Study/project specific decisions

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

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which "*must*" lead to discontinuation of patient from trial.

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
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment 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). This contrasts with the slightly

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more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

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

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

4.5 Programming rules

The following should be used for programming of efficacy results:

4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

4.5.5 Study/project specific programming

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

4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 3-2)
- Death due to reason other than underlying cancer (only used for TTP and duration of response)
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-

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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.

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14.2 Appendix 2: irRECIST

1 Introduction

Immune-related response criteria have been developed to better assess the patterns of response and progression with cancer immunotherapies (Wolchok et al. 2009, Nishino et al. 2013, 2014). This document outlines the working definitions and rules for immune-related response criteria based on RECIST 1.1 (irRECIST).

For definition of measurable and non-measurable lesions, methods of tumor measurement, baseline documentation of target and non-target lesions, eligibility based on measurable disease, follow-up evaluation of lesions, etc., refer to RECIST 1.1 (Appendix 1).

2 Baseline assessment of tumor burden

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. All other lesions present at baseline will be considered as non-target lesions. Together these present the baseline tumor burden.

The Total Measurable Tumor Burden (TMTB) at baseline is defined as the sum of diameters (SOD) of all target lesions.

3 Post-baseline assessment of tumor burden

Target, non-target and new lesions (measurable and non-measurable) will be evaluated at each post-baseline assessment. Target and non-target lesions identified at baseline will continue to be followed as target and non-target lesions, respectively. New measurable lesions will be included in the TMTB which is defined as the SOD of target lesions and the new measurable lesions for post-baseline assessments. The nadir TMTB at a given time point ‘n’ is defined as the smallest TMTB observed for a given patient up to, but excluding that time point (i.e. from baseline to timepoint ‘n-1’).

A new measurable lesion is a newly observed lesion that was not present at baseline tumor assessment and is measurable as per RECIST 1.1. Overall a maximum of five new measurable lesions (nodal or non-nodal) can be included in the TMTB with a maximum of two new measurable lesions per organ. If there are more than 5 new measurable lesions in total, or more than 2 in the same organ at a post-baseline tumor evaluation, then the largest and most reproducible new measurable lesions should be included in TMTB. Note that two new measurable lesions per organ can be included in the TMTB irrespective of whether baseline target lesions were already identified in that organ or not. All other new lesions will be included in the overall tumor burden assessment as new non-measurable lesions.

A new measurable lesion included in the TMTB must always be included in TMTB for all subsequent tumor assessments. A new non-measurable lesion will always be followed as a non-measurable lesion at subsequent tumor assessments even if it becomes measurable.

The overall tumor burden (OTB) includes the TMTB, non-target lesions and new non-measurable lesions.

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4 Overall response assessment

An overall response assessment should occur at each post-baseline assessment, and will take into account the evaluation of the TMTB together with the status of non-target lesions and new non-measurable lesions.

Baseline non-target lesions

The response of non-target lesions primarily contributes to the overall response assessment of complete response (irCR), with persisting non-target lesions preventing irCR. Only a clear and unequivocal worsening of non-target lesions alone (i.e. worsening of the tumor burden which is substantial enough leading to discontinuation or change of therapy), would be indicative of irPD.

New lesions

A new lesion does not automatically indicate progressive disease.

New measurable lesions are added to the SOD to obtain the TMTB as described in Section 14.2.3 at each post-baseline tumor evaluation. All new lesions not selected as new measurable lesions for obtaining TMTB are considered as new non-measurable lesions and are followed qualitatively. Only an unequivocal progression of new non-measurable lesions (i.e. worsening of the overall tumor burden which is substantial enough leading to discontinuation or change of therapy) would be indicative of irPD. Persisting new non-measurable lesions prevent irCR.

Note: The designation of overall irPD solely on the basis of change in non-target disease or new non-measurable lesions in the face of no progression based on TMTB is expected to be uncommon.

4.1 Definition of response categories

The response categories at each post-baseline assessment are defined as follows:

- **Immune related Complete Response (irCR)**: Complete disappearance of all measurable and non-measurable lesions. In addition, any pathological lymph nodes must have a reduction in short axis to < 10 mm.
  - TMTB may be greater than zero at the time of CR, if nodal lesions are included in TMTB.
  - 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 determine the irCR.
- **Immune related Partial Response (irPR)**: At least 30% decrease in the TMTB compared to baseline and not qualifying for irPD or irCR
- **Immune related Progressive Disease (irPD)**: At least a 20% increase in the TMTB compared to nadir. In addition to the relative increase of 20%, TMTB must also demonstrate an absolute increase of at least 5 mm. An unequivocal progression of existing non-target or new non-measurable lesions may also lead to irPD.

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- **Immune related Stable Disease (irSD)**: Neither a sufficient shrinkage to qualify for irPR or irCR, nor an increase in lesions, or a clear and unequivocal progression of existing non-target or new non-measurable lesions that would qualify for irPD.

  - **Unknown for irRECIST (irUNK)**: Progression has not been documented and one or more target lesions or new measurable lesions observed at earlier assessment have not been assessed, or have been assessed using a significantly different method (i.e. prevents reasonable comparison to the prior assessments) than baseline (target lesions) or assessment of first occurrence (new measurable lesions). Note that if non-target or new non-measurable lesions have not been assessed at any given post-baseline time-point, then this will not lead to overall response irUNK. If the evaluation of any non-target lesion or new non-measurable lesion is not done, and all target lesions and other non-target lesions disappeared, irCR cannot be determined and overall response must be "irPR".

Table 4-1 Overall response at each post-baseline assessment

Target and new measurable lesions based on (TMTB), * (%)	Non-target lesions and New non-measurable lesions	Overall lesion response
- 100 [a], [b]	Absent	irCR
- 100 [a], [b]	Stable/not evaluated	irPR
≤-30 [b]	Absent/Stable/not evaluated	irPR
>-30 [b] and< +20 [c]	Absent/Stable/not evaluated	irSD
≥+20 [c]	Any	irPD
Any	Unequivocal progression [e]	irPD

[a] TMTB may be greater than zero at the time of irCR, if nodal lesions are included in TMTB
[b] Compared to baseline
[c] Compared to nadir
[d] If worsening of non-target or new non-measurable lesions is substantial enough leading to discontinuation or change of treatment.

4.1.1 Notes on lesion response

Reappearance of lesions

If the lesion reappears 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 the previous disappearance of the lesion is confirmed, then the investigator/radiologist has to decide between the following possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment should consider this appropriately either as a new measurable or new non-measurable lesion.
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in the Table above. This applies to patients who have not achieved target response of irCR. For patients who have achieved irCR, please refer to below.

Progressive disease after complete response

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Similar to RECIST 1.1, following a confirmed irCR, an irPD can subsequently only be assigned if any one of below is observed:

- Either a non-nodal target or new-measurable lesion that disappeared earlier reappears at the same anatomical location.
- Any single nodal lesion gets >10mm in diameter and there is at least 20% increase in sum of the diameters of all nodal target and nodal new-measurable lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- Unequivocal progression based on non-target and new non-measurable lesions.

Missing measurements

In cases where measurements are missing for one or more target or new-measurable lesions it is sometimes still possible to assign irPD 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 an irPD should be assigned. However, in other cases where an irPD cannot definitely be attributed, the target lesion response would be irUNK.

Nodal lesions

- 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.
- 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 nodal lesions less than 10 mm are considered normal, an irCR for target lesion response based on TMTB should be assigned when all nodal target and new-measurable lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.

Splitting and coalescence of lesions

- Lesions split: In some circumstances, disease that is measurable as a target or new-measurable lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions at subsequent assessments. 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 based on TMTB. The individual split lesions will not be considered as new lesions.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at earlier assessment(s) 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

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a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.

4.2 Confirmation of response or progression

Confirmation of irCR and irPR is required by a repeat assessment at least 4 weeks after the initial assessment.

Confirmation of irPD is highly recommended particularly for difficult cases (i.e. mixed response, early appearance of new lesions/increase in measurable tumor burden in patients with stable or improving general status/clinical condition) or suspected pseudo-progression/tumor flare provided there is no rapid clinical deterioration. The irPD is confirmed if in a repeat tumor assessment at least 4 weeks later meets again the irPD criteria as defined in Section 4.1.

No confirmation is required for irSD.

4.3 Determination of Best overall response

For best overall response (BOR), in general all the details as specified in the RECIST 1.1 appendix Section 14.1.3.1 will apply unless stated otherwise below or in the study protocol.

The best overall response for each patient is determined from the sequence of overall responses according to the following rules:

- irCR = at least two determinations of irCR at least 4 weeks apart before confirmed progression. Note that there should not be any tumor assessment with an overall response of irPD in between
- irPR = at least two determinations of irPR or better at least 4 weeks apart before confirmed progression (and not qualifying for irCR). Note that there should not be any tumor assessment with an overall response of irPD in between
- irSD = at least one irSD assessment (or better) > 6 weeks after randomization/start of treatment and before confirmed progression (and not qualifying for irCR or irPR).
- irPD = confirmed immune related progression or immune related progression with no further adequate tumor assessments £ 12 weeks after randomization/ start of treatment (and not qualifying for irCR, irPR or irSD)
- irUNK = all other cases (i.e. not qualifying for confirmed irCR or irPR and without irSD after more than 6 weeks or early progression within the first 12 weeks)
- If the next tumor assessment is inadequate with an overall response of irUNK then the next adequate tumor assessment will be considered for confirmation. E.g. an irCR followed by irUNK followed by irPR will be a confirmed irPR.

Similar to RECIST 1.1 overall lesion response of irCR or irPR, after their confirmation, will remain the same or improve until confirmed irPD.

5 Only non-measurable disease at baseline

For patients with only non-measurable disease at baseline, unequivocal progression of non-target lesions (i.e. worsening of the overall tumor burden which is substantial enough leading to discontinuation or change of therapy) will constitute an irPD. In addition, the appearance of new lesions (measurable or non-measurable) consistent with unequivocal progression taking

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into account the overall disease burden will constitute an irPD. The absence of all non-target lesions and no new lesions will qualify for irCR. Otherwise the overall response will be considered as irNon-CR/Non-PD (irNCRNPD) similar to RECIST 1.1. The same rules for confirmation of irPD and irCR apply as specified above in Section 4.3. If any baseline non-target lesion or a new lesions observed at an earlier post-baseline evaluation was not/could not be assessed at a later post-baseline tumor evaluation then the overall response will be irUNK.

No confirmation is required for irNCRNPD. For the BOR the same definition as in Section 14.2.4.3 applies for irCR, irPD and irUNK. For BOR of irNCRNPD the definition for irSD will be used.

6 Definition of endpoints

Immune related overall response rate (irORR) is the proportion of patients with a best overall response of irCR or irPR. This is also referred to as 'Objective response rate' in some protocols or publications.

Immune related disease control rate (irDCR) is the proportion of patients with a best overall response of irCR or irPR or irSD. Patients with BOR of irNCRNPD will also be included in DCR if patients with non-measurable disease at baseline are in analysis set.

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

Immune related early progression rate (irEPR) is the proportion of patients with immune related progressive disease (irPD) within 12 weeks of the start of treatment.

6.1 Time to event endpoints

6.1.1 Progression-free survival

Immune related progression-free survival (irPFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented assessment of irPD that was then confirmed or death due to any cause. Unconfirmed irPD without further adequate tumor assessments will be considered as a confirmed irPD. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment. An adequate tumor assessment is a tumor assessment with overall response other than irUNK. Refer to RECIST 1.1 appendix for additional details on censoring rules.

6.1.2 Time to progression

Immune related time to progression (irTTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented assessment of irPD that was then confirmed or death due to underlying cancer. Unconfirmed irPD without further adequate tumor assessments will be considered as a confirmed irPD. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment. An adequate tumor assessment is defined as a tumor assessment with overall response other than irUNK. Refer to RECIST 1.1 appendix for additional details on censoring rules.

6.1.3 Time to treatment failure

Immune related time to treatment failure (irTTF) is the time from date of randomization/start of treatment to the earliest of date of progression (confirmed irPD), date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol deviation' or 'Technical problems'. Unconfirmed irPD without further adequate tumor assessments will be considered as a confirmed irPD. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment. An adequate tumor assessment is defined as a tumor assessment with overall response other than irUNK.

6.1.4 Time to response

Immune related time to overall response (irCR or irPR) (irTTR) is the time between date of randomization/start of treatment until first documented response (confirmed irCR or irPR). Time to overall response will be censored for patients without confirmed irCR or irPR as described in RECIST 1.1 appendix.

6.1.5 Duration of response

Immune related duration of overall response (irCR or irPR) (irDOR): For patients with a confirmed irCR or irPR the start date is the date of first documented confirmed response 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 are observed.

Immune related duration of overall complete response (irCR): For patients with a confirmed irCR the start date is the date of first documented confirmed irCR and the end date and censoring is defined the same as that for time to progression.

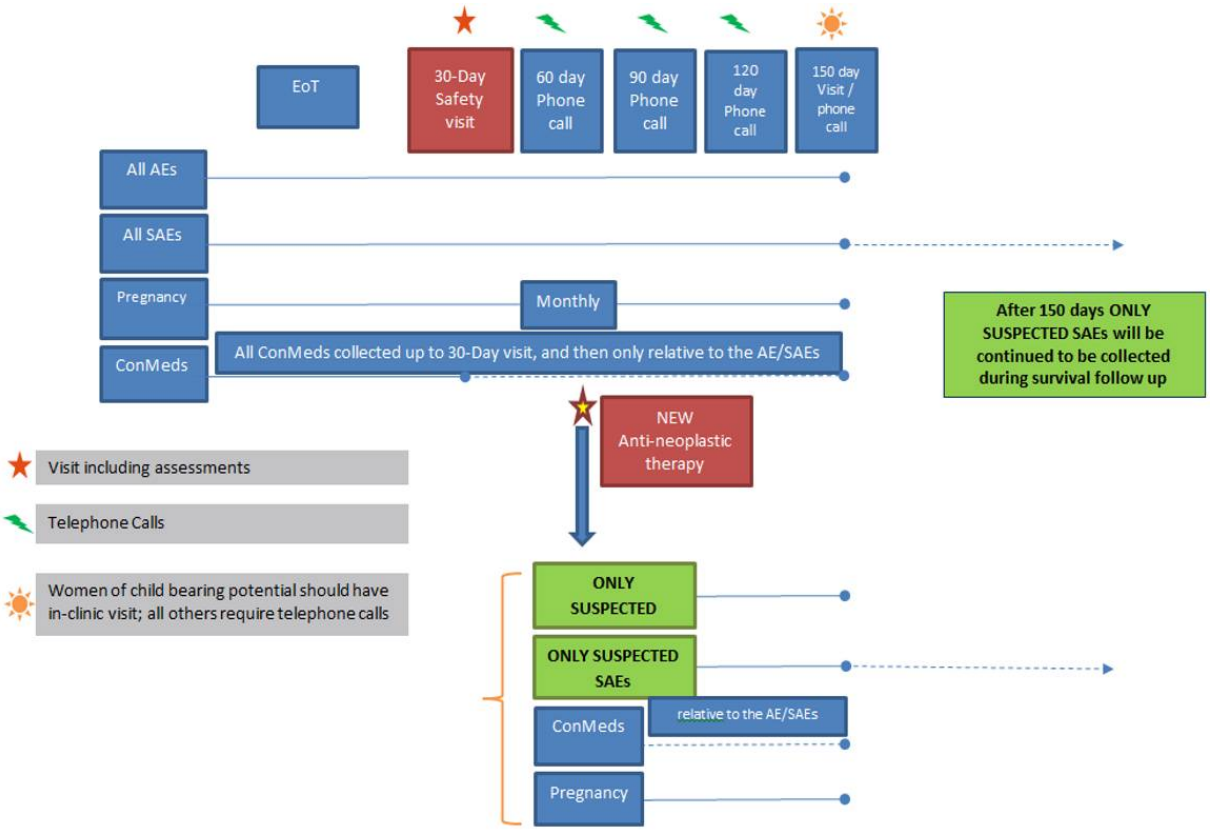
Immune related duration of stable disease (irCR/irPR/irSD): For patients with BOR of irCR (confirmed) or irPR (confirmed) or irSD the start and end date as well as censoring is defined the same as that for time to progression.

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

For the definition related to time to event variables refer to RECIST 1.1 Appendix 1 Section 4.5.1.

[redacted]

14.3 Appendix 3: Safety follow-up flowchart



[redacted]