

Clinical Development

PDR001

Protocol CPDR001X2101 / NCT02404441

Open label multicenter Phase I/II study of the safety and efficacy of PDR001 administered to patients with advanced malignancies

Statistical Analysis Plan (SAP) Amendment 3

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Amendment 1	3July2018	<ol style="list-style-type: none">1. Updated document names to the current conversion throughout the document2. Added the Q3W dosing schedule in the study design, added the potential change to an alternative dosing schedule, updated the study design of Phase II part and added the study design figure in Phase I part in Section 1.13. Added specification of the primary endpoint for Phase I part and more [REDACTED] endpoints per protocol in Section 1.24. Updated the general description of data analysis and the treatment grouping definition for Phase I and Phase II in Section 1.35. Unified the use of “study treatment” throughout the document6. Moved the definition of End of Study to Section 2.1.27. Added baseline definition for some rare cases in Section 2.1.3.28. Added specific definition of observation period in Section 3.59. Added the definition of end date of the last cycle for Q3W schedule and modified that for Q2W and Q4W in Section 2.1.3.410. Declared a listing for data from screen failure patients in Section 2.311. Changed the timing of PK data to evaluate the $AUC_{(0-336h)}$ to be in cycle 3 per protocol in the definition of DDP, Table 2-1, and Section 3.3.1.1.112. Added ATC to protocol deviation INCL05 in Table 2-213. Added a section for “Withdrawal of Informed Consent” as Section 2.3.814. Added a listing of EOT details in Section 3.1.115. Provided more specific description of the demographic summary in Section 3.1.216. Updated the variables for “Diagnosis and extent of cancer” in Section 3.1.417. Provided more details of summary of prior antineoplastic therapy in Section 3.1.518. Added a table of PDs in Section 3.1.619. Added rules for date imputation of the first and last administration in Section 3.2.1.1.1 and Section 3.2.1.2.1, respectively20. Added the definition of last date of exposure for Q3W schedule and modified that for Q2W and Q4W in Section 3.2.1.321. Updated the definition of actual and planned cumulative dose in Section 3.2.1.822. Updated the units for DI and PDI in Section 3.2.1.923. Modified the summary of duration of exposure, accumulative dose, DI and PDI in Section 3.2.2

Version	Date	Changes
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Version	Date	Changes
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Addendum 2	07-July-2020	<ol style="list-style-type: none"> 1. Update a typo in the section with the PK analysis details. The word "<i>plasma</i>" was updated to the word "<i>serum</i>" – Section 3.6
Amendment 3	24-July-2020	<ol style="list-style-type: none"> 1. Update reference to protocol amendment 8. 2. Update the analysis specification for DOR for the Phase I part of the study. Only mean, minimum and maximum will be used to summarized DOR in the Phase I.

List of abbreviations


AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
APC	Antigen Presenting Cell
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anaplastic thyroid cancer
AUC	Area Under the Curve
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
CNS	Central Nervous System
CRC	Colorectal Cancer
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSF	Colony Stimulating Growth Factor
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dosage administration record
DCR	Disease Control Rate
DDP	Dose Determining Pharmacokinetic Set
DDS	Dose-Determining Safety Set
DI	Dose intensity
DLT	Dose Limiting Toxicity
DOR	Duration of Response
EBV	Epstein Barr Virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
ER	Estrogen Receptor
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FIH	First In Human
FU	Follow-up
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HER2	Human Epidermal growth factor Receptor 2
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
i.v.	Intravenous(ly)
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFN- γ	interferon-gamma
IG	Immunogenicity
IHC	Immunohistochemistry
IL-2	Interleukin-2
IL-6	Interleukin-6
IRB	Institutional Review Board
irRC	immune related Response Criteria

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Patient Number (Patient No.)	A unique identifying number assigned to each patient who enrolls in the study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
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 discontinuation	Point/time when a patient permanently discontinues study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

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1 Introduction

This Statistical Analysis Plan (SAP) provides the detailed statistical methodology for the analysis of data from study CPDR001X2101 that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the TFL shells document. The specifications for derived variables and datasets can be found in the Programming Datasets Specifications (PDS) document. This version of the SAP is based on Protocol Amendment 8.

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

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

1.1 Study design

This study is a Phase I/II, multi-center, open-label study starting with a Phase I dose-escalation part followed by a Phase II part. PDR001 is administered intravenously (i.v.) every 2, 3 or 4 weeks with a weight-based dosing in Phase I dose-escalation part and with flat dosing in Phase II part until a patient experiences unacceptable toxicity, progressive disease as per irRC, and/or treatment is discontinued at the discretion of the Investigator or the patient. Patients should not discontinue treatment based solely on progressive disease per RECIST v1.1. The study design is summarized in [Figure 1-1](#).

Phase I dose-escalation part

During the Phase I part of the study, cohorts of patients are treated with PDR001 in mg/kg, until the MTD is declared or a lower RP2D is established. The RP2D will be a dose that results in PDR001 exposure (as measured by AUC) that is comparable to the exposures of Pembrolizumab and Nivolumab at their recommended doses. To assure that the RP2D does not exceed the MTD, the dose escalation is guided by an adaptive Bayesian logistic regression model (BLRM) following the escalation with overdose control (EWOC) principle. At least 21 patients are required during dose escalation to define the MTD; however, fewer than 21 patients may be treated if the RP2D is determined prior to reaching the MTD (for further details see [\[CPDR001X2101 Amendment 8 Section 6.2.3\]](#)).

Phase II part

Once the MTD and/or RP2D is declared, additional patients will be enrolled in the Phase II part in order to assess the preliminary anti-tumor activity of PDR001.

In the phase II part, patients will be assigned to different groups depending on the tumor type and dosing regimen as shown in [Figure 1-1](#). Please refer to [\[CPDR001X2101 Amendment 8 Section 5.1\]](#) for further details.

Groups 1a, 1b and 2 will treat approximately 60 patients each, group 3 will treat approximately 40 patients, and group 4 will treat approximately 10 patients. Enrollment to any of these groups

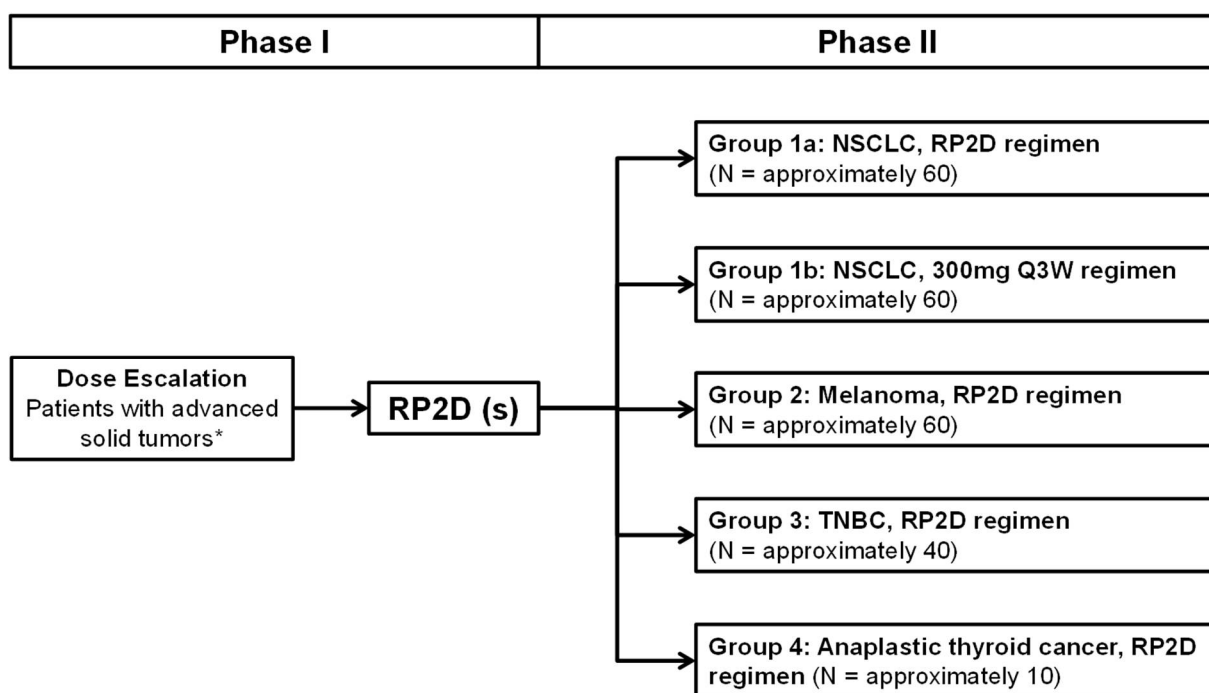
may be stopped with fewer patients if achieving these enrollment targets is not logistically feasible. The relatively small size of the anaplastic thyroid cancer group reflects the low prevalence of anaplastic thyroid cancer; this group may be increased in size to approximately 40 patients based on feasibility of enrollment and if PDR001 appears to be active (at least one response or other efficacy data show preliminary anti-tumor activity in the first 10 patients) in this disease. A Bayesian design will be used in order to estimate ORR within each group. Details of the sample size calculations leading to the patient numbers are provided in [\[CPDR001X2101 Amendment 8 Section 10.8\]](#).

After a preliminary assessment of the safety profile in the phase I part, a decision may be made to test up to two regimens of PDR001 during the phase II part to better assess the efficacy, safety and benefit-risk of PDR001. If a second regimen is to be studied, then this would be done in one or more disease indications chosen based in part on logistical feasibility. The two regimens would be assigned in an alternating fashion to patients of the same disease group across all the sites in this global study. The number of patients tested at this second regimen will be similar to the number of patients to be enrolled in this disease setting at the RP2D.

Potential change to flat dosing during the phase II part

If emerging PK data indicate that a flat or fixed dose of PDR001 is appropriate, then a flat dosing may be implemented in the phase II part of the study. The data from weight-based dosing obtained during the dose escalation part of the study will be utilized to identify the flat dose to be tested in the phase II part.

Figure 1-1 Study design



* In the dose escalation, at least 21 patients are required to define the MTD; however, fewer than 21 patients may be treated if the RP2D is achieved prior to determination of the MTD. One of the RP2Ds may be the MTD.

After a preliminary assessment of the safety profile in the phase I part, a decision may be made to test up to two regimens of PDR001 during the phase II part.

1.2 Objectives and endpoints

Objectives and related endpoints are described in [Table 1-1](#) below.

Table 1-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
Phase I part: To estimate the RP2D and/or the MTD for PDR001	Phase I part: <ul style="list-style-type: none"> The exposure ($AUC_{(0-336h)}$) after first dose of treatment at cycle 3 The incidence of DLTs 	3.3.1
Phase II part: To estimate the anti-tumor activity of PDR001	Phase II part: Overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1).	3.3.2
Secondary		
Phase I/II parts: To characterize the safety and tolerability of PDR001	Safety: Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including changes in laboratory parameters, vital signs and electrocardiograms (ECGs) Tolerability: Dose interruptions, reductions and dose intensity	3.5
Phase I/II parts: To characterize the pharmacokinetic profile of PDR001	Serum PK parameters (e.g., AUC, Cmax, Tmax, half-life); Serum concentration vs. time profiles	3.6
Phase I/II parts: To assess emergence of anti-PDR001 antibodies following one or more intravenous (i.v.) infusions of PDR001	Presence and/or concentration of anti-PDR001 antibodies	3.7
Phase I part: To evaluate the preliminary anti-tumor activity of PDR001	ORR, progression free survival (PFS), duration of response (DOR) and disease control rate (DCR)	3.4
Phase II part: To evaluate the preliminary anti-tumor activity of PDR001	ORR per immune related Response Criteria (irRC), PFS, DOR, DCR	3.4

1.3 Data Analysis

All statistical analysis will be performed under the direction of Novartis personnel using the most updated SAS® version in the GPS environment. For analyses using R and/or WinBUGS (e.g., Bayesian analysis) the most updated version in the MODESIM environment will be used

PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 6.4.

Any data analysis carried out independently by the Investigator should be submitted to Novartis prior to publication or presentation.

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

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

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

- For Phase I, cohorts treated with the same dose level and schedule of PDR001 will be pooled into a single treatment group. All summaries, listings, figures and analyses for patients in Phase I will be performed by treatment group, unless otherwise specified.
- For Phase II, all summaries, listings, figures and analyses will be performed by disease and treatment group (dose level and regimen of PDR001) if more than one treatment is tested.
- In order to simplify the writing, the statement of “by treatment” or “by treatment group” will imply the above definition for grouping for Phase I and Phase II accordingly, throughout the rest of this document, unless re-defined otherwise in specific cases.

Note: patients from the Phase I dose escalation and the Phase II will not be pooled in any analyses unless otherwise specified.

1.3.1 Data included in the analyses

Analyses for the dose-escalation part will be based on all patients’ data up to the time when all patients have either completed at least one cycle of treatment or have discontinued due to DLTs. To determine the MTD, only DLTs that occur during Cycle 1 and patients belonging to the Dose-determining safety set (DDS) ([\[CPDR001X2101 Amendment 8 Section 2.3.4\]](#)) will be considered for inclusion into the Bayesian models in the dose-escalation part.

Dose-escalation meetings

At each dose-escalation meeting results from the adaptive Bayesian linear model for dose-exposure and the adaptive BLRM for DLT analysis will be provided. In order to provide a timely response, these results are based upon information provided by the clinical team, rather than data held in the clinical database.

Primary CSR

The primary clinical reporting of the dose escalation, and each of the Phase II indications will take place when all patients in the escalation, or relevant indication have discontinued, or completed at least six cycles of treatment. This time can be indication specific, therefore a single primary CSR, or several primary CSRs may be prepared which may include more than one indication.

Final CSR

Any additional data for patients continuing on study past the data cut-off for the corresponding primary CSR, as allowed by the protocol, will be summarized in a subsequent final CSR.

2 Definitions and general methodology

2.1 General definitions

2.1.1 Study treatment related definitions

Study treatment: refers to the Novartis investigational drug PDR001. The terms “study drug”, “study treatment” and “study medication” are used interchangeably. For the purpose of consistency, the term “study treatment” will be used throughout this document.

PDR001 is provided to investigational sites as 100 mg powder for solution for infusion in vial open label bulk medication.

Dose regimen: PDR001 is administered i.v. every 2 weeks (Q2W) or every 3 weeks (Q3W) or every 4 weeks (Q4W).

2.1.2 Other definitions

Cohort: a group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time in the Phase I dose-escalation part. Cohorts are not expanded, new cohorts are enrolled.

Treatment group: patients coming from different cohorts but being treated at the same dose level/schedule. Treatment groups are determined by the initially planned PDR001 dose level on Cycle 1 Day 1. A treatment group can include several cohorts of patients who received the same dose level/schedule but were recruited at a different point during the study.

Dose-limiting toxicity: an AE or abnormal laboratory value of CTCAE grade ≥ 3 assessed as unrelated to disease, disease progression, inter-current illness or concomitant medications, which occurs within the first cycle of treatment with PDR001 during the Phase I dose escalation part of the study, with the exceptions described in [\[CPDR001X2101 Amendment 8 Table 6-3\]](#).

Maximum tolerate dose (MTD): the highest safe dose of PDR001 given as a single agent for a given schedule that causes DLTs in no more than 33% of patients during the first cycle of treatment (28 days).

End of treatment (EOT): at any time, patients may voluntarily withdraw from the study or be removed from it at the discretion of the Investigator. The primary reasons for EOT are AEs; disease progression; protocol violation /deviation; patient withdrew consent; lost to follow up; administrative problems; death.

Patients who discontinue study treatment for any reason (except death) were to be scheduled for an EOT visit within 14 days at which time all of the assessments listed on [\[CPDR001X2101 Amendment 8 Table 7-1\]](#) for EOT visit were to be performed.

End of study (EOS): the end of the study will be when 80% of the patients per disease group in the Phase II part have completed the follow-up for disease progression or discontinued the study for any reason, and all patients have completed treatment and the 150 day safety follow-up period, or if the study is terminated early. The definition is for the planned time point to end this study.

2.1.3 Assessment windows, baseline and post baseline definitions, missing data handling

2.1.3.1 Study day

The study day for all post-treatment assessments (e.g. efficacy and safety) is calculated as the difference between the date of the event (visit date, onset date of an event, assessment date, etc.) and the date of first administration of non-zero dose of study treatment plus one day. The first day of study treatment is therefore Study Day 1.

The study day for all pre-treatment assessments is calculated as the difference between the date of the event and the date of first administration of non-zero dose of study treatment. The last day prior to PDR001 administration is therefore Study Day -1. For the particular case of pre-treatment assessments performed on the day of first administration, the study day is set to Day 1.

Unless specified otherwise, the study day is displayed in the data listings.

2.1.3.2 Baseline

Baseline is the result of an investigation describing the “true” state of the subject before start of study treatment administration.

Baseline (e.g. for laboratory parameters) is considered as the last non-missing assessment or value before start of the first treatment, unless otherwise stated under the related assessment.

Baseline could be within 21 days (or 28 days for radiological evaluations) before first treatment administration or on the same day as first treatment administration if specified pre-dose (e.g., ECG).

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

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

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last value should be considered as baseline.

Patients with no data on a particular parameter before the first treatment administration will have a missing baseline for this parameter.

For ECG evaluations three serial 12-lead ECGs will be obtained on Cycle 1 Day 1 for each patient, prior to the first administration of PDR001 (C1D1). The average of the triplicate ECG measurements will serve as the patient's baseline value for post-dose comparisons.

2.1.3.3 On-treatment assessment/event and observation periods

The overall observation period is 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 treatment
2. on-treatment period: from day of first dose of study treatment to 30 days after last dose of study treatment
3. post-treatment period: starting at day 31 after last dose of study medication.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). Following last administration of PDR001, adverse events (including serious adverse events), and new antineoplastic therapies are collected for a period of 150 days. Following start of new antineoplastic therapy, only study treatment related adverse events are collected. Select summaries of related adverse events will be produced for the combined on-treatment and post-treatment periods ([Section 3.5.2.2](#)).

2.1.3.4 Cycle day and duration definition

A treatment cycle is defined as 28 days for the Q2W and Q4W regimens and 21 days for the Q3W regimen, for the purposes of scheduling procedures and evaluations.

Several visits are scheduled for each cycle [[CPDR001X2101 Amendment 8 Table 7-1](#)]. For all visits, there is a ± 7 days window on assessments. Laboratory assessments that are completed within 3 days prior to C1D1 do not need to be repeated on C1D1.

The respective cycle number and day within cycle will be re-derived according to the following rules:

- C1D1 coincide with the start date of treatment.
- All pre-treatment assessments are displayed as Cycle 0 with a negative day (e.g., Day -1 is the day before the patient started treatment), or Cycle 1 Day 1 for assessment performed pre-dose on the day of the first administration of study treatment.
- Day 1 of a cycle corresponds to the day reported by investigator on the start of cycle.
- For all cycles but the last, the end date of a cycle is defined as the day before Day 1 of the following cycle as recorded.
- In the situation where a patient received the whole treatment cycle as planned (e.g., Cycle 1 for 4 weeks) but had an additional rest period (e.g., 1 week) in order to recover from AEs

before next cycle start, duration of cycle is then longer than originally planned (e.g., 5 weeks).

- The end date of the last cycle is when treatment administration is permanently discontinued at the latest of the following days:
 - Date of last administration + 13 days for Q2W schedule;
 - Date of last administration + 20 days for Q3W schedule;
 - Date of last administration + 27 days for Q4W schedule.
- All post-cycle assessments are displayed as follow-up and with, by analogy, Day 1 representing the first day after the end of the last cycle.
- The duration (in days) of a cycle is defined as: cycle end date – cycle start date + 1. Cycle number and day within cycle are computed to be displayed in listings only.

2.1.3.5 Windows for analysis

Windows to be used for summaries of PK concentrations by scheduled time point are described in [\[CPDR001X2101 Amendment 8 Section 7.2.3\]](#), however, if outside the time window, these will not be excluded unless flagged by the CP expert – a comment would then be provided. Unless otherwise specified, when more than one assessment is available for a visit, all assessments will be listed under the visit while only the assessment closest to the planned day for the visit will be used for summaries and analyses.

2.2 Imputation rule of partial or missing dates/data

Imputation rule of partial or missing dates

As a general rule, when a date is recorded as a partial date, the missing day is imputed to the 15th of the month (e.g., DEC2007 imputed to 15DEC2007), and if the day and month are both missing then to July 1st of that year (e.g., 2007 imputed to 01JUL2007). Such imputed data are flagged in the listings.

Imputation rules for AEs, medical history and concomitant medications partial or missing dates are defined in [Section 4.1.1](#).

In order to be conservative, these rules tend to maximize the duration of AEs under treatment and are equivalent to the rule above otherwise.

For other partial dates, the general STL standard imputation rules are used.

For computation of time intervals (e.g. elapse time between initial diagnosis to first recurrence/relapse), if the imputation rule leads to a negative value, time interval should be set to missing.

Handling of missing values/censoring/discontinuation

Continuing events (e.g. AEs) will be summarized using the data cut-off date as the date of completion, with an indication within listings that the event is continuing. For patients who discontinue the study with ongoing events, the discontinuation date is used as the completion date of the event with the appropriate censoring.

The reasons for discontinuation from study will be listed, along with dates of first and last study treatment, and date of discontinuation for each patient.

Other missing data will simply be noted as missing on appropriate tables/listings.

2.3 Analysis sets

A patient must have given informed consent to participate in the study before being included in any analysis set.

Patients will be excluded from the analysis sets based on the protocol deviations and specific non-protocol deviations entered in the database. All protocol deviations and non-protocol deviations leading to exclusion from specific analysis set will be identified before database lock.

See [Table 2-1](#) for non-protocol deviation leading to exclusion from analysis set definitions, and [Table 2-2](#) for protocol deviation leading to exclusion from analysis set definitions.

All protocol deviations will be listed by treatment.

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reasons for not being started on treatment will be entered on the Screening Log eCRF, and each patient's demographic information will be recorded on the Demography eCRF. For these patients, the eCRF data collected will not be included in analyses, but will be reported in the CSR as separate listings.

The following analysis sets are defined for the analysis of the study data.

2.3.1 Full analysis set

The Full Analysis Set (FAS) includes all patients who received at least one dose of PDR001. Patients will be analyzed according to the planned treatment (dose level and regimen). The FAS will be used for all listings of raw data. Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

2.3.2 Safety set

The Safety Set (SS) includes all patients from the FAS who have received at least one dose of PDR001 and had at least one valid post-baseline safety assessment. The statement that a patient had no AEs (on the AE eCRF) constitutes a valid safety assessment. Patients will be classified according to treatment received, where treatment received is defined as:

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

The safety set will be used for the safety summary of the study.

2.3.3 Per-Protocol set

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

- Presence of at least one measurable lesion at baseline according to RECIST v1.1 as per [Appendix 1](#) in [[CPDR001X2101 Amendment 8](#)]

- At least 2 post-baseline tumor assessments (unless disease progression is observed before that time)
- Have not been previously treated with PD-1- or PD-L1-directed therapy

Patients will be classified according to treatment received.

The PPS will be used in the Phase II part of the study only and will define the patients used in the sensitivity analysis of the primary endpoint [CPDR001X2101 Amendment 8 Section 10.4.4]. If the PPS and the FAS are identical, then analyses described by the PPS in study protocol will not be performed.

2.3.4 Dose-determining safety set

The dose-determining safety set (DDS) consists of all patients from the safety set in Phase I dose escalation who either meet the following minimum exposure criterion and have sufficient safety evaluations, or have experienced a DLT during Cycle 1. A patient is considered to have met the minimum exposure criterion if he/she receives at least 70% of the planned dose of PDR001 at each time of dosing during Cycle 1.

Patients who do not experience DLT during Cycle 1 are considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

Patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for the DDS and an additional patient may be recruited (see [CPDR001X2101 Amendment 8 Section 7.1.4.1]).

2.3.5 Dose-determining pharmacokinetic analysis set

The dose-determining pharmacokinetic set (DDP) consists of all patients in the Phase I dose escalation part who have received at least one dose of PDR001 during Cycle 1 and have sufficient PK data in cycle 3 to evaluate the $AUC_{(0-336h)}$. DDP will only be used for analysis of study treatment exposure.

2.3.6 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable PK data. The PAS will be used for summaries of PK concentration data, and PK parameters, except that DDP will be used in the dose-exposure analysis in the Phase I dose-escalation part.

Note: Patients may be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of analysis. Any concentration data and PK parameter data resulting from non-evaluable profile will only be listed in data listings but will not be included in summary tables and figures.

2.3.7 Immunogenicity (IG) analysis sets

The Immunogenicity prevalence set includes all subjects in the Full analysis set with a determinant baseline IG sample **or** at least one determinant post-baseline IG sample.

The Immunogenicity incidence set includes all subjects in the Immunogenicity prevalence set with a determinant baseline IG sample **and** at least one determinant post-baseline IG sample.

See Section 3.8.1 for the definition of determinant.

2.3.8 Analysis set exclusion

Patients will be excluded from the analysis sets based on the protocol deviations and specific non-protocol deviations entered in the database. All protocol deviations and non-protocol deviations leading to exclusion from specific analysis sets will be identified before database lock. Protocol and non-protocol deviations leading to exclusion from specific analysis sets and reasons for exclusion from populations will be tabulated/listed by treatment (Phase I) /indication and treatment (Phase II).

Table 2-1 displays non-protocol deviations leading to exclusion from analysis set definitions and Table 2-2 displays protocol deviations leading to exclusion from analysis set definitions.

Table 2-1 Non-protocol deviation leading to exclusion from analysis set definitions

Summary of non PD	Analysis set(s) to be excluded
No valid post-baseline safety assessment	SS
No administration of study treatment	FAS, SS, PPS, DDS, DDP, PAS, Immunogenicity prevalence set, Immunogenicity incidence set
1. Patient, who has not experienced DLT, was not observed for ≥ 28 days following the C1D1 or had not completed the required safety evaluations for Cycle 1 or 2. Patient who has not experienced DLT, received <70% planned doses at each time of dosing in Cycle 1.	DDS
The patient did not receive at least one dose of PDR001 during cycle 1 or did not have sufficient PK data in cycle 3 to evaluate the $AUC_{(0-336h)}$.	DDP
Patient did not have at least one measurable PDR001 concentration in cycle 1	PAS
No determinant IG sample at both baseline and post-baseline	Immunogenicity prevalence set
No determinant IG sample at baseline or post-baseline or both	Immunogenicity incidence set

Table 2-2 Protocol deviation leading to exclusion from analysis set definitions

Protocol Deviation ID (DVSPID)	Summary of PD	Analysis set(s) to be excluded
INCL01	Written informed consent must be obtained prior to screen procedures.	FAS, SS, PPS, DDS, DDP, PAS, Immunogenicity prevalence set, Immunogenicity incidence set

Protocol Deviation ID (DVSPID)	Summary of PD	Analysis set(s) to be excluded
INCL04	In the Phase II part, patient does not have at least one tumor lesion meeting measurable disease criteria as determined by RECIST v1.1.	PPS
INCL05	In the Phase II part, patient was not a patient with either NSCLC, melanoma, TNBC, or ATC.	PPS

2.3.9 Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

Additional data for which there is a separate informed consent, e.g. PK, biomarker etc., collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.3.10 Subgroup analyses

Select summaries of efficacy will also be presented by treatment and will be based on PD-L1 expression with predefined thresholds ([Section 3.7](#)).

2.4 Sample size and power considerations

Please refer to [[CPDR001X2101 Amendment 8 Section 10.8](#)].

2.5 Interim analyses

No formal interim analyses are planned. However, the dose-escalation design foresees that decisions based on the current data are taken before the EOS. More precisely, after each cohort in the Phase I dose-escalation part, the next dose is to be chosen depending on the observed data.

3 Statistical methods used in reporting

3.1 Patient disposition, background and demographic characteristics

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

3.1.1 Patient disposition

The following patient disposition information will be listed and summarized by treatment group for all patients in FAS at time of reporting.

- Enrolled patients who remained on treatment or discontinued treatment at the time of cut-off
- EOT: Primary reasons for EOT based on EOT eCRF
- EOS: Study evaluation completion after EOT:
 - Patients who are either no longer being followed up for study evaluation or who continued to be followed for study evaluation based on EOT eCRF

A listing of EOT details will be produced. Patients enrolled but not treated will be listed along with the reason for discontinuing from the study. Screen failures will not be included in any of the summary tables, but will be reported in separate listings.

3.1.2 Demographic characteristics

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data, e.g. gender, age groups: 18 - <65 years and \geq 65 years, race, ethnicity, weight categories: <55, 55 - <75, and \geq 75 kg, ECOG performance status, will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data, e.g. age, weight, height, will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

3.1.3 Medical History

Relevant and current medical history will be summarized and listed. The summaries were to be presented by primary system organ class and preferred term and coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting.

3.1.4 Diagnosis and extent of cancer

Diagnosis and extent of cancer (disease history) will be summarized for the following variables: diagnosis of disease, details of tumor histology/cytology, histologic grade, stage at initial diagnosis, time (in months) since initial diagnosis, time (in months) from initial diagnosis to first recurrence/relapse, time (in months) since most recent recurrence/relapse to treatment start, types of lesions (target and non-target lesions) at baseline, current extent of disease (metastatic sites).

Due to the imputation method for partially missing dates, the time intervals indicated above could be computed as negative. In such situation, they must be handled as missing dates.

Patient listings with disease history details will be provided.

3.1.5 Prior anti-neoplastic therapy

All prior anti-neoplastic medication, radiotherapy and surgery will be listed.

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

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), therapy type at last treatment, setting at last treatment, time (in days) from last treatment to progression, best response at last treatment (defined to be the best response during the last treatment regimens recorded). Prior

antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical class, and preferred term.

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

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

3.1.6 Protocol deviations

The FAS will be used for the protocol deviation summary tables and listing. The number (%) of patients with any CSR-reportable protocol deviation will be tabulated by the deviation category (selection criteria not met, study treatment deviation, not discontinued after meeting withdrawal criteria, use of prohibited concomitant medicine and other deviation). The full list of CSR-reportable protocol deviations is documented in the Study Specification Document (SSD). All protocol deviations will be listed by treatment.

3.2 Treatments (study treatment, concomitant therapies and compliance)

Study treatment is PDR001.

3.2.1 Study treatment exposure

The safety set is used for all summary tables and listings for drug exposure.

3.2.1.1 Date of first administration of study treatment

The date of first administration of study treatment is defined as the first date when a nonzero dose of study treatment (PDR001) was administered and recorded on the PDR001 dosage administration record (DAR) electronic case report form (eCRF). This date is also referred to as start date of study treatment.

3.2.1.1.1 Date imputation of the first administration of study treatment

Subjects with missing start dates are generally considered missing for all study treatment related calculations described in [Section 3.2.1.4](#) and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

However, if the dosing information at C1D1 is entered on the PK DAR page, the date on this page will be used to impute the first administration date. Before imputing the date, it will be checked that the date is not after the second administration or after the end date of the first record.

3.2.1.2 Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a nonzero dose of study treatment (PDR001) was administered and recorded on the DAR eCRF. This date is also referred to as last date of study treatment.

3.2.1.2.1 Data imputation for the last administration

The following rule should be used for the imputation of date of last administration for study treatment:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page, the subject is considered as on-going:

The subject should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT visit:

Use last day of the Month (mm).

After imputation, compare the imputed date with the start date of that specific record, if the imputed date is < start date of that record

Use the start date of that record.

3.2.1.3 Last date of exposure to study treatment

PDR001 every 2 weeks (Q2W) administration:

Last date of exposure = min(last date of administration of PDR001 + 13 days, death date, cut-off date).

PDR001 every 3 weeks (Q3W) administration:

Last date of exposure = min(last date of administration of PDR001 + 20 days, death date, cut-off date).

PDR001 every 4 weeks (Q4W) administration:

Last date of exposure = min(last date of administration of PDR001 + 27 days, death date, cut-off date).

3.2.1.4 Duration of study treatment exposure

The following algorithms will be used to calculate the duration of study treatment exposure (in days and in cycles) for patients taking at least 1 dose of the study treatment:

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

Duration of exposure (cycles) = calculate the duration of exposure as stated above and then consider the patients exposed to the study treatment for one cycle if he/she received at least 70% of the planned dose of PDR001 within the cycle.

For patients who did not take any study treatment, the duration of exposure is defined as zero.

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

3.2.1.5 Dose delay/interruption

Any dose change/delay flagged in the DAR eCRF page, satisfying the following criteria:

- a reason other than “as per protocol”
- a zero actual dose
- occurs between the first and last non-zero doses
- follows a nonzero actual dose.

3.2.1.6 Dose reduction

Any dose change/delay flagged in the DAR eCRF page, satisfying the following criteria:

- a reason other than “as per protocol”
- a nonzero actual dose below the immediate previous nonzero actual dose,
- a non-zero actual dose below the treatment assigned as per safety set.

3.2.1.7 Dose increment

Any dose change/delay flagged in the DAR eCRF page, satisfying the following criteria:

- a reason other than “as per protocol”,
- a nonzero actual dose above any previous nonzero actual dose ,
- a nonzero actual dose above the treatment assigned as per safety set .

The following criteria will be used to identify an **intra-patient dose escalation**:

- dose change flag checked with reason “as per protocol”,
- planned dose above any previous planned dose.

3.2.1.8 Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure.

The **actual cumulative dose** for study treatment (PDR001) is defined as the total actual dose for this study treatment administrated, over the duration for which the subject is on the study treatment as documented in the DAR eCRF.

The following algorithms will be used to calculate the actual dose per one infusion in mg:

- For weight based dosing: Actual dose (mg) = (Calculated dose prescribed, mg) × (Total volume administrated, ml) / (Total volume constituted, ml)

- For flat dosing: $\text{Actual dose(mg)} = (\text{Dose prescribed, mg}) \times (\text{Total volume administered, ml}) / (\text{Total volume constituted, ml})$

These parameters used for calculation ('Calculated dose prescribed', 'Dose prescribed', 'Total volume constituted', 'Total volume administered') will be collected on the DAR eCRF page. For patients who did not take any of study treatment, the actual cumulative dose is by definition equal to zero. Actual cumulative dose will then be calculated as the sum of actual dose per one infusion for all infusions.

The **planned cumulative dose** is defined as the total dose planned to be given as per the protocol up to the last date of study treatment administration. It is calculated in mg as:

- For weight based dosing: $\text{Planned cumulative dose (mg)} = \text{sum of (Calculated dose prescribed, mg) for all infusions}$
- For flat dosing: $\text{Planned cumulative dose (mg)} = \text{sum of (Dose prescribed, mg) for all infusions.}$

Similarly, 'Calculated dose prescribed' and 'Dose prescribed' will be collected on the DAR eCRF page. The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

3.2.1.9 Dose intensity and relative dose intensity

For PDR001, the dose intensity (DI), expressed as mg/day, for patients with non-zero duration of exposure is defined as follows:

Dose intensity (DI) (mg/day) = actual cumulative dose (mg) / duration of exposure (days).

Planned dose intensity (PDI) (mg/day) = planned cumulative dose (mg) / duration of exposure (days).

Relative dose intensity (RDI) is the actual DI divided by the PDI, i.e. $\text{RDI} = \text{DI(mg/day)} / \text{PDI(mg/day)}$.

For patients who do not take any study treatment, the actual cumulative dose is by definition equal to zero.

3.2.2 Study treatment

The duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment group for the safety set.

To assess tolerability, dose delay and dose reduction for the study treatment will be summarized by treatment group. By-patient listings will be provided.

Summary of duration of exposure of study treatment will include categorical summaries (based on clinically meaningful time intervals like < 4 weeks, 4 – 8 weeks, 8 – 12 weeks, >= 12 weeks etc.) and continuous summaries (i.e. mean, standard deviation etc) using appropriate units of time.

The actual cumulative dose of the study treatment, DI, RDI and RDI categories to measure compliance will be summarized with descriptive statistics by treatment. The predefined

categories for RDI are < 0.5 , $\geq 0.5 - < 0.75$, $\geq 0.75 - < 0.9$, $\geq 0.9 - < 1.1$ and ≥ 1.1 . The number and proportion of patients within each category will be presented by treatment group.

The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by treatment. Patient level listings of all doses administered on treatment along with dose change reasons will be produced.

3.2.3 Prior and concomitant therapies

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

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

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see [Section 3.5.2](#) Adverse events). No imputation will be performed for concomitant medication end dates.

3.3 Analysis of the primary variable(s)

3.3.1 Phase I: dose-escalation part

The primary objective for the Phase I dose-escalation part of this study is to estimate the MTD and/or RP2D of PDR001 in adult patients with advanced solid tumors. Dose recommendation and estimation of the RP2D/MTD during the dose-escalation part of the study will be supported by the following co-primary variables:

- The $AUC_{(0-336h)}$ after first dose of treatment in cycle 3 for patients in the DDP.
- The incidence of DLTs in the first cycle of treatment for patients in the DDS.

The corresponding primary analysis for dose-escalation is based on an adaptive Bayesian linear regression of PDR001 exposure and Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle using the methodology described in detail in [\[CPDR001X2101 Amendment 8 Section 10.4.2\]](#).

All tables and listings will be presented by treatment in which data from different Phase I cohorts treated with the same dose and schedule will be pooled in the CSR.

The final RP2D for future development will be based on considerations of the PDR001 exposure, the BLRM for DLT, and overall clinical assessment of all available safety, tolerability, and PK data from all cycles at all different dose levels tested.

3.3.1.1 Statistical hypothesis, model, and method of analysis

The dose escalation will be guided by both PDR001 exposure and the DLT rate. Details of the guidelines for dose escalation and determination of the RP2D/MTD are provided in [\[CPDR001X2101 Amendment 8 Section 6.2.3\]](#).

3.3.1.1.1 Dose Exposure Bayesian Linear Regression Model

Dose-exposure relationships will be estimated for PDR001 via the following dose-exposure Bayesian linear model, in order to guide the dose recommendation to targeted exposures of PDR001.

$$\log(\text{AUC}_i) = \log(\alpha) + \beta \log(d_i/d^*) + \varepsilon_i, \quad \alpha > 0, \beta > 0 \quad [1]$$

where $i = 1, \dots, n$ is the i -th patient in the study, d_i is the dose received by the i -th patient, AUC_i is the area under the curve of PDR001 concentrations for the i -th patient during the interval of 0 to 336 hours after the first dose of treatment in cycle 3. The residual error ε_i follows a Normal distribution with mean of 0 and variance σ^2 . Doses are rescaled as d_i/d^* with reference dose $d^*=3$ mg/kg of PDR001. The prior distributions for parameters $\log(\alpha)$, $\log(\beta)$, and σ are derived based on published summary data of Nivolumab and Pembrolizumab (Robert 2014, Deeks 2014).

From the estimation of the Bayesian linear model, the following posterior summaries will be derived for each dose level of PDR001:

- Mean, median, standard deviation and 95%-credible interval for the exposure of PDR001, as measured by $\text{AUC}(0-336\text{h})$ after first dose of treatment in cycle 3.
- The probability that the true $\text{AUC}(0-336\text{h})$ after first dose of treatment in cycle 3 achieves the target exposure, as measured by $\text{AUC}(0-336\text{h}) \geq 1000 \mu\text{g} \cdot \text{day}/\text{ml}$.

Prior specifications

The meta-analytic-predictive (MAP) approach was used to derive an informative prior for $\log(\alpha)$, $\log(\beta)$, and σ from published AUC data on Nivolumab and Pembrolizumab. For details on the MAP approach see Neuenschwander et al. (2010), Schmidli et al (2014).

The MAP distributions were derived. A normal distribution was used to approximate the MAP distribution for $\log(\sigma)$. For the regression coefficients ($\log(\alpha)$, $\log(\beta)$), a three-component multivariate normal mixture distribution was used to approximate the derived MAP distribution. To allow for more robust inference in case of the discrepancy between MAP information and the trial data, a non-informative prior component was added as the 4th component. The respective distribution for each component and its weight is provided in Table 3-1.

Table 3-1 Prior distribution of (log(Alpha), log(Beta)) and σ for the new trial

Parameter	Means	Standard deviations	Correlation	Weight
Component 1:				
$\log(\alpha), \log(\beta)$	(6.40, 0.05)	(0.683, 0.180)	-0.463	0.480
Component 2:				
$\log(\alpha), \log(\beta)$	(6.38, 0.05)	(0.403, 0.118)	-0.773	0.425
Component 3:				
$\log(\alpha), \log(\beta)$	(6.42, 0.05)	(1.410, 0.257)	-0.217	0.095
Prior for σ:	LN(-0.97, 0.317 ²)			

For further details on the Bayesian linear model including the prior specification for the model parameters along with simulation results that show the operating characteristics of the Bayesian linear model design, refer to [CPDR001X2101 Amendment 8 Appendix 3-Section 14.3.1].

If the dose-exposure does not follow a linear relationship in the natural log scale, non-linear curves will be assessed via data visualization and/or non-linear modeling.

3.3.1.1.2 Reports of dose-exposure relationship

A plot of predicted AUC during the interval of 0 to 336 hours after the first dose of treatment in cycle 3 with 95% CI will be produced based on the dose determining pharmacokinetic set.

3.3.1.1.3 BLRM for DLTs

In addition to the Bayesian linear model, an adaptive, 2 parameter Bayesian logistic regression model (BLRM) will be used to estimate the probability of a DLT in the first cycle of treatment. The prior distributions for the BLRM are derived based on available pre-clinical data and clinical data for Nivolumab and Pembrolizumab.

The dose-toxicity relationship in the dose escalation part of the study will be described by the following logistic regression model:

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*), \quad \alpha > 0, \beta > 0 \quad [2]$$

where $\text{logit}(\pi_{(d)}) = \log(\pi_{(d)}/(1-\pi_{(d)}))$, and $\pi_{(d)}$ is the probability of a DLT at dose d . Doses are rescaled as d/d^* with reference dose $d^*=3$ mg/kg of PDR001. As a consequence α is equal to the odds of DLT rate at d^* . Note that for a dose equal to zero, the probability of toxicity is zero.

Prior specifications

This study uses a mixture prior consisting of two components.

Table 3-2 Prior distribution of model parameters

Parameter	Means	Standard deviations	Correlation	Weight
Component 1: weakly informative priors				
$\log(\alpha), \log(\beta)$	-2.692, -1.26	1.0, 1.0	0	0.8
Component 2: priors for a more toxicity sensitive population				
$\log(\alpha), \log(\beta)$	-2.3, 0	2, 1	0	0.2

For further details on the BLRM model including the model structure, the prior specification for the model parameters, and examples of hypothetical decisions that may be followed during the dose escalation, refer to [\[CPDR001X2101 Amendment 8 Appendix 3-Section 14.3.2\]](#).

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels are obtained. The results of this analysis are summarized in terms of the probability that the true rate of DLT at each dose level lies in each of the following categories:

- [0, 16%) under-dosing
- [16%, 33%) targeted toxicity
- [33%, 100%] excessive toxicity

Dose recommendation will also be guided by the EWOC principle, which mandates the dose for the next cohort to have less than 25% chance of excessive toxicity. The final estimate of the RP2D/MTD will also satisfy this condition.

In case of changes in dosing schedule during dose-escalation, a BLRM of the same functional form described in [\[CPDR001X2101 Amendment 8 Appendix 3\]](#) will be used to estimate the

dose-DLT relationship for each schedule based on a newly derived prior incorporating the historical trial data and the on-study data from previous schedule. At each time the model is updated, all available information on the dose-DLT relationship from all explored dosing schedules will be used. In order to account for between schedule variability in the assessment of a given dosing schedule, the DLT data obtained from other explored dosing schedules will be down-weighted.

Change in dosing schedule

In the event of a change in dosing schedule, then a new BLRM will be set up. This new BLRM will have the same functional form as equation [2] and will incorporate down-weighted existing dose escalation data in the prior distribution (see [CPDR001X2101 Amendment 8 Section 14.3] for technical details). For comparability, the dose for the new and old model will be in mg/kg per cycle.

For a Q4W schedule, the doses of PDR001 will be rescaled (doses are multiplied by 1/2). In addition, the information from Q2W will be incorporated by down-weighting the data directly using the following weight “w”: (Chen and Ibrahim 2006, Neuenschwander et al 2010):

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

where n is the sample size of historical data, σ is the “outcome standard deviation” for one observation and τ is the between trial standard deviation. σ is the standard deviation of all data from one historical trial which may include several dose levels. For the Q4W schedule, σ was chosen as 2 and τ was set as 0.5 to correspond to moderate between-trial variability with the Q2W schedule. Note that the weights can also be expressed as a function of n and n_{∞}^* , the maximum prior effective sample size under infinite historical information for which

$$n_{\infty}^* = \frac{\sigma^2}{\tau^2}$$

3.3.1.1.4 Reports of DLT analysis

Following reports will be produced based on the dose determining safety set:

- A plot of posterior interval probabilities will be presented in the body of the CSR;
- Summary of the DLTs with onset during the evaluation period (dose escalation part only) by primary system organ class, preferred term: recommendations at the time of database lock will be included in the body of the CSR, for each dose escalation meeting (DEM), summary of recommendations will be included in Appendix 16.1.9 of the CSR;
- Listing of inferential results from the BLRM at the time of database lock, will be included in Appendix 16.1.9.

3.3.2 Phase II part

The Phase II part of the study will be conducted in adult patients enrolled in multiple indications. The analysis will be using ORR reported per RECIST v1.1 to estimate the anti-tumor activity of PDR001. A Bayesian analysis will be used to estimate the true ORR based on the observed ORR within each group, and it will be used to provide inferential summaries (e.g., mean, median,

interval probabilities) in relation to the patient population for each of the disease groups (defined in [CPDR001X2101 Amendment 8 Section 5.2]).

For a Bayesian design, 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 populations 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 conservatively set to be equal to 20% and the parameters of the minimally informative Beta prior distribution of ORR have been set up as follows:

- $a/(a+b) = 0.2$
- $a = 0.25$
- $b = 1.0$

At primary analysis, this prior distribution will be updated with all the data available from the patients in the FAS. See sample size estimation in [CPDR001X2101 Amendment 8 Section 10.8].

Groups 1a, 1b and 2 (NSCLC and melanoma): Estimates of the ORR for each group along with mean, median, standard deviation, and 95% credible intervals and the interval probabilities for the true ORR lying within [0%, 15%), [15%, 20%), [20%, 30%), [30%, 50%) and [50%, 100%] will be presented.

If the observed ORR is equal to or greater than 20% (i.e. ≥ 12 responses (CR or PR) out of 60 patients) for NSCLC and 30% (i.e. ≥ 18 responses (CR or PR) out of 60 patients) for melanoma, then this will be considered as preliminary evidence of activity of PDR001 in the respective groups.

Note that for a sample size of $n = 60$,

- for NSCLC (group 1a or 1b), if the observed ORR is 20%, then the posterior probability of true ORR greater than 15% is 83.7%.
- for melanoma, if the observed ORR is 30%, then the posterior probability of true ORR greater than 20% is 96.2%.

Groups 3: Estimates of the ORR for each group along with mean, median, standard deviation, and 95% credible intervals and the interval probabilities for the true ORR lying within the intervals stated below will be presented:

- [0, 10%) unacceptable efficacy
- [10, 20%) limited efficacy
- [20, 30%) moderate efficacy
- [30%, 100%] clinically relevant efficacy

Group 4 (Anaplastic thyroid cancer): Estimates of the ORR along with mean, median, standard deviation, and 95% credible intervals and the interval probabilities for the true ORR lying within the intervals stated below will be presented.

- [0, 5%) unacceptable efficacy
- [5, 10%) limited efficacy
- [10, 20%) moderate efficacy

- [20%, 100%] clinically relevant efficacy.

3.4 Efficacy evaluation

Analysis of efficacy endpoints will be performed using the FAS.

Assessment by irRC

For irRC (see [CPDR001X2101 Amendment 8 Appendix 14.2]) the key difference from RECIST v1.1 (see [CPDR001X2101 Amendment 8 Appendix 14.1]) in the assessment of these endpoints is the recommendation that irPD be confirmed at least 4 weeks after the criteria for irPD are first met. A single assessment of irPD followed by a subsequent assessment of irSD or better will be considered as a pseudo-progression, these are not considered as progression events for the purposes of analysis. Where irPD is confirmed by a second assessment, the date of the first of these two assessments is then the date of progression. For patients who have ended treatment without a valid confirmation assessment, for the purposes of analysis the single assessment of irPD will be treated as a confirmed irPD. At time of analysis there may be patients whose last adequate assessment is an unconfirmed irRC progression but who are continuing treatment. In these cases that progression will be treated as a confirmed progression for the primary analysis, and sensitivity analysis of time to event endpoints may be conducted in which the patient is censored at the time of last adequate assessment. Additional definitions and derivation rules for irRC are provided in [Section 4.2](#).

Best overall response (BOR)

The BOR is the best response recorded from the start of the treatment until disease progression/recurrence. For RECIST v1.1 and irRC, any assessments taken before the start of any further antineoplastic therapy will be considered in the assessment of BOR in recognition that response to immunotherapy may be delayed. For both RECIST v1.1 and irRC, if any alternative antineoplastic therapy is taken while on study, any subsequent assessments will be excluded from the BOR determination.

Per RECIST v1.1, CR and PR need to be confirmed with at least two determinations of CR or PR respectively at least 4 weeks apart before progression. In order to classify overall response as SD, a patient must have at least one SD assessment (or better) > 6 weeks after start date of study treatment. In order to classify overall response as PD, a patient must have progression < 12 weeks after start date of study treatment.

Per irRC, irCR, irPR and irPD need to be confirmed with at least two determinations of irCR or irPR or irPD, respectively at least 4 weeks apart. In order to classify overall response as irSD, the patient must have at least one SD assessment (or better) > 6 weeks after start date of study treatment.

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. Best overall response (BOR) per RECIST v1.1 and per irRC will be listed and tabulated.

Overall response rate (ORR) and Disease control rate (DCR)

ORR is the proportion of patients with a best overall response of CR or PR (RECIST v1.1) or of irCR or irPR (irRC). DCR is the proportion of patients with a best overall response of CR, PR, or SD (RECIST v1.1) or of irCR, irPR, or irSD (irRC).

Progression free survival (PFS)

For assessment per RECIST v1.1, PFS is the time from date of 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, PFS is censored at the date of last adequate tumor assessment ([CPDR001X2101 Amendment 8 Appendix 14.1.3.2.1]). For irRC, PFS is defined similarly, but with the date of event defined as the date of the first documented confirmed progression as defined in Section 4.2.3, or death due to any cause. For irRC, other censoring rules are applied as for RECIST v1.1 ([CPDR001X2101 Amendment 8 Appendix 14.1.3.2.9]).

Duration of response (DOR)

DOR applies only to patients with a BOR of confirmed CR or PR (RECIST v1.1) or of confirmed irCR or irPR (irRC). For assessment per RECIST v1.1, DOR is defined as the time from the date of the first documented response (CR or PR) to the date of first documented progression, or death due to any cause. For assessment per irRC, DOR is defined as the time from the first confirmed response (irCR or irPR), to the date of confirmed progression as defined in Section 4.2.3, or death due to any cause.

[REDACTED]

[REDACTED]

Use of alternative cancer therapy

For both RECIST v1.1 and irRC, if any alternative cancer therapy is taken other than palliative radiotherapy any subsequent assessments will be excluded from the analysis of endpoints based on tumor response assessments. If a substantial number of patients receive palliative radiotherapy, sensitivity analyses of these endpoints may be performed where assessments are also censored at the time of palliative radiotherapy.

3.4.1 Phase I: dose-escalation part

Tumor response will be determined per local investigators' assessment, according to RECIST v1.1 and irRC. Response related efficacy assessments will be defined and analyzed based on both RECIST v1.1 and irRC. The endpoints used to evaluate anti-tumor activity are BOR, ORR, DCR, PFS [REDACTED]

For all efficacy parameters, data will be listed, summarized, or analyzed by treatment group.

BOR will be summarized. ORR and DCR will be listed and summarized with accompanying 90% exact binomial confidence intervals.

If appropriate, PFS will be presented graphically using Kaplan Meier plots including all patients treated at RP2D/MTD and by treatment group. Median PFS (in months), 25th and 75th percentiles with corresponding 90% CIs and Kaplan-Meier estimated probabilities (PFS rate) with corresponding 90% CIs at 3, 6, 9, and 12 months will be estimated for each treatment group. DOR will be summarized using the mean, minimum and maximum. PFS, along with DOR for patients who experience a CR or PR at any time on study, will be listed by patient.

[REDACTED]

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. Best overall response per RECIST v1.1 and per irRC will be listed and tabulated.

3.4.2 Phase II part

Tumor response will be determined per local investigators' assessment, according to RECIST v1.1 and irRC. Response related efficacy assessments will be defined and analyzed based on both RECIST v1.1 and irRC. The endpoints used to evaluate anti-tumor activity are BOR, ORR, DCR, DOR, PFS using the FAS.

For all efficacy parameters, data will be listed, summarized, or analyzed by treatment group in Phase II.

BOR will be summarized. ORR and DCR will be summarized and listed with accompanying 90% exact binomial confidence intervals. The waterfall plot of best percent change in the sum of longest diameter (SOD) since baseline with annotation of the BOR for RECIST v1.1 will be provided.

PFS will be listed by patient. PFS (per RECIST v1.1 and irRC) will be presented graphically using Kaplan Meier plots including all patients treated at RP2D/MTD and by treatment in Phase II. Median PFS (in months), 25th and 75th percentiles with corresponding 90% CIs and Kaplan-Meier estimated probabilities (PFS rate) with corresponding 90% CIs at 3, 6, 9, and 12 months will be estimated and summarized for each treatment group. The number (%) of events and subjects censored will also be summarized.

DOR will be listed by patient. If there is a large number of patients achieving response (for example, at least 8 responses in a treatment group), the Kaplan-Meier plots for DOR (per RECIST v1.1 and irRC) will also be produced along with the estimation of the respective medians.

3.5 Safety evaluation

All safety analyses will be based on the Safety Set. The only exceptions will be the summaries of dose limiting toxicities (DLTs) for which the DDS will be used and presented by treatment.

The overall observation period is 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 treatment
2. on-treatment period: from day of first dose of study treatment to 30 days after last dose of study treatment
3. post-treatment period: starting at day 31 after last dose of study treatment.

Safety summaries will primarily be based on all data from the on-treatment period. Following last administration of PDR001, adverse events (including serious adverse events), and new antineoplastic therapies are collected for a period of 150 days. Following start of new antineoplastic therapy, only study treatment related adverse events will be collected. Select summaries of related adverse events will be produced for the combined on-treatment and post-treatment periods ([CPDR001X2101 Amendment 8 Section 10.5.3.2]).

3.5.1 Dose- limiting toxicities

In the Phase I dose-escalation part, DLTs are listed by primary system organ class, worst grade based on the CTCAE version 4.03, and by dose cohort. The Dose determining safety set is used for this summary. By-patient listings will be provided.

3.5.2 Adverse events

3.5.2.1 Data handling

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, respectively.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

If CTCAE grading does not exist for an AE, grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE grade 5 (death) is not used in this study. Death information will be collected on the “Death” eCRF pages.

3.5.2.2 Data analysis

AE Summaries (CSR outputs)

Primary AE summaries will include all AEs that started or worsened during the on-treatment period. Additional select summaries will be produced using all treatment related AEs starting or worsening during the on-treatment or post-treatment period.

All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study treatment, AE outcome etc. AEs starting during the pre- or post-treatment periods will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the ‘All grades’ column of the summary tables.

In AE summaries the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in all patients.

The following adverse event summaries will be produced by treatment for AEs starting or worsening during the on-treatment period:

- Overview of adverse events and deaths (number and % of subjects who died, with any AE, any SAE, any dose reductions/interruptions, AE leading to discontinuation)
- AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment);
- Seriousness (SAEs, and non-SAEs);
- Leading to treatment discontinuation;
- Leading to dose interruption/adjustment;
- Requiring additional therapy;
- Leading to fatal outcome;
- Dose limiting toxicities by PT

The following summaries will be produced for all AEs starting or worsening during the on-treatment or post-treatment periods:

- AEs related to study treatment by SOC and PT;
- SAEs related to study treatment

The following listings will be produced:

- All adverse events (safety set)
- Adverse events among subjects who were not treated (all screened subjects)

Deaths (CSR Outputs)

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by system organ class and preferred term.

All deaths will be listed for the safety set, deaths occurring after the on-treatment period will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set population in the final CSR.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship, will be provided by PT.

3.5.2.3 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound PDR001. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of subjects with at least one event of the AESI occurring during on-treatment period will be summarized.

Summaries of these AESIs will be provided by primary system organ class and/or preferred term and treatment.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

3.5.3 Laboratory data

3.5.3.1 CTC grading for laboratory parameters

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

3.5.3.2 Imputation rules

CTC grading for blood differentials is based on absolute values.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

$$\text{xxx count} = (\text{WBC count}) * (\text{xxx \%value} / 100)$$

Corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

$$\text{Corrected Calcium (mg/dL)} = \text{Calcium (mg/dL)} - 0.8 [\text{Albumin (g/dL)} - 4]$$

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium are as defined in the previous section.

3.5.3.3 Data analysis

On analyzing laboratory, data from all sources (central and local laboratories *(as applicable)*) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see [Section 2.1.3.3](#)).

The following listing will be produced for the laboratory data:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE 4.03 grades if applicable and the classifications relative to the laboratory normal ranges

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

For laboratory tests where grades are defined by CTCAE 4.03:

- 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 4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE 4.03:

- Shift tables using the low/normal/high/ (low and high)

[Table 3-3](#) lists all laboratory parameters for which CTCAE grades are defined.

Table 3-3 Laboratory parameters to be listed and presented in grade shift tables based on CTC grade

Hematology and coagulation		Biochemistry	
White Blood Cells (WBC)	↑↓	Albumin	↓
Hemoglobin	↓	Alkaline phosphatase	↑
Platelets counts	↓	ALT (SGPT)	↑
Absolute Neutrophils	↓	AST (SGOT)	↑
Absolute Lymphocytes	↑↓	Glucose	↑↓

activated partial thromboplastin time (APTT)	↑	Calcium	↑↓
International normalized ratio (INR)	↑	Total Bilirubin	↑
		Creatinine	↑
		Potassium	↑↓
		Magnesium	↑↓
		Sodium	↑↓

↑ Indicates that CTC grade increases as the parameter increases, these parameters are to be included in the summary of maximum post-baseline lab parameters

↓ Indicates that CTC grade increases as the parameter decreases, these parameters are to be included in the summary of minimum post-baseline lab parameters

Table 3-4 lists all laboratory parameters to be listed based on local laboratory normal ranges.

Table 3-4 Laboratory parameters to be listed based on local laboratory normal ranges

Hematology and coagulation	Biochemistry
Absolute eosinophils	Urea
Absolute basophils	Blood urea nitrogen (BUN)
Absolute monocytes	Direct bilirubin
	Indirect bilirubin
	Bicarbonate
	Chloride
	T4
	TSH
	IL-6
	IFN-γ

3.5.3.4 Hematology

Hematologic tests include: a complete blood count (CBC) consisting of a total white blood cell count (WBC) with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), hemoglobin, and platelet count.

Differential counts will be converted to absolute values for CTC grade classification. For all the differential counts, percentages will be converted to absolute values, if necessary:

e.g. Absolute WBC diff (Wunit) = Absolute WBC (Wunit)*Relative WBCdiff(%)/100.

3.5.3.5 Biochemistry

Biochemistry includes the following parameters: urea or blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, albumin, direct and total bilirubin, alkaline phosphatase, AST,

ALT, glucose, magnesium, chloride, bicarbonate,, inorganic phosphate, urinalysis, thyroid function (T4, TSH) and cytokines (IL-6, IFN- γ).

3.5.4 Thyroid function tests

Thyroid function tests include the following parameters: Thyroid stimulating hormone, Thyroxine (total T4) and T4 Free. The change from baseline to worst value post baseline will be summarized.

3.5.5 Vital signs, weight and physical examinations

Vital sign assessments are performed in order to characterize basic body function. The following parameters are collected: weight (kg), body temperature ($^{\circ}$ C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Vital signs collected during on-treatment period will be summarized. Values measured during the post-treatment period will be flagged in the listings. The number and percentage of patients with notable vital sign values (high/low) will be presented by treatment. For analysis of vital signs, the clinically notable sign criteria are provided in [Table 3-5](#).

Table 3-5 Criteria for notable vital sign values

Vital sign (unit)	Notable high value	Notable low value
Weight (kg)	increase \geq 10% from baseline	decrease \geq 10% from baseline
Systolic blood pressure (mmHg)	\geq 180 and increase from baseline of \geq 20	\leq 90 and decrease from baseline of \geq 20
Diastolic blood pressure (mmHg)	\geq 105 and increase from baseline of \geq 15	\leq 50 and decrease from baseline of \geq 15
Pulse rate (bpm)	\geq 100 and increase from baseline of \geq 25%	\leq 50 and decrease from baseline of \geq 25%
Body temperature ($^{\circ}$ C)	\geq 39.1	--

3.5.6 Electrocardiograms

The average of the ECG parameters at that assessment should be used in the analyses.

A listing of all ECG assessments will be produced by treatment and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

The number and percentage of subjects with notable ECG values will be presented by treatment (see [Table 3-6](#)).

Table 3-6 Notable ECG values

ECG Parameter	Abnormal values
QT, QTcF and QTcB	New value of $>$ 450 and \leq 480 ms New value of $>$ 480 and \leq 500 ms New value of $>$ 500 ms Increase from baseline of $>$ 30 ms to \leq 60 ms Increase from baseline of $>$ 60 ms

HR	Decrease from baseline >25% and to a HR < 50 beats/min Increase from baseline >25% and to a HR >100 beats/min
PR	Increase from baseline >25% and to a value >200 ms New value of > 200 ms
QRS	Increase from baseline >25% and to a value >120 ms New values of QRS > 120 ms

3.5.7 ECG

ECOG performance by treatment will be listed.

3.6 Pharmacokinetic data

Pharmacokinetic parameters of PDR001 will be determined using serum concentration only. Pharmacokinetic (PK) parameters for Phase II portion of the study will be determined for all PK-evaluable patients using non-compartmental method(s) using WinNonlin (Pharsight, Mountain View, CA).

All serum concentrations that are below the limit of quantification (BLQ) will be set to zero in the bioanalytical data.

The PK parameters displayed on [Table 3-7](#) will be estimated and listed. All concentrations below the LLOQ, or any missing data, will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics. The “zero” values will be excluded from geometric mean calculation.

PAS will be used in all pharmacokinetic data analysis and PK summary statistics, except for the dose-exposure analysis in Phase I.

Table 3-7 Noncompartmental pharmacokinetic parameters

Variable	Definition (unit)
C _{max}	Maximum observed concentration after drug administration [mass x volume ⁻¹] (ug/mL)
T _{max}	Time to reach C _{max} [time] (days)
AUC _(0-336h)	Area under the concentration-time curve from time 0 to 336 hours post-dose [mass x time x volume ⁻¹] for Q2W (ug*hr/mL or ug*day/mL)
AUC _(0-504h)	Area under the concentration-time curve from time 0 to 504 hours post-dose [mass x time x volume ⁻¹] for Q3W (ug*hr/mL or ug*day/mL)
AUC _(0-672h)	Area under the concentration-time curve from time 0 to 672 hours post-dose [mass x time x volume ⁻¹] for Q4W (ug*hr/mL or ug*day/mL)
AUC _{inf}	The AUC from time zero to infinity (ug*hr/mL or ug*day/mL)
AUC _{tau} *	Area under the concentration-time curve over the dosing interval [mass x time x volume ⁻¹] (ug*hr/mL or ug*day/mL)
R _{acc} *	Accumulation ratio calculated as AUC _(0-336h) or AUC _{tau} at cycle 3/ AUC _(0-336h) or AUC _{tau} at cycle 1
CL	The total body clearance of drug from the serum [volume x time ⁻¹] (mL/hr)

Variable	Definition (unit)
Vz	The apparent volume of distribution during terminal phase (associated with λ_z) [volume] (mL)
Tlast	Time to last measurable concentration (days)
T1/2	Elimination half-life (days)

*AUCtau will be estimated if data permits and in case of assessing the alternate dosing regimen. With cohorts of patients with Q3W dosing regimen, AUCtau (or AUC_{0-504h}) will be reported instead of AUC_(0-336h) and also will be used to calculate Racc. With cohorts of patients with Q4W dosing regimen, AUCtau (or AUC_{0-672h}) will be reported instead of AUC_(0-336h) and also will be used to calculate Racc.

The PK data may be combined with data from other trials for a population PK analysis and reported separately.

Early analysis of preliminary PK data may be conducted based on preliminary data prior to database lock. Planned dose instead of actual dose will be used; nominal time instead of actual elapsed time will be used, and no protocol deviations or other PAS exclusion criteria will be considered.

Descriptive statistics and graphical representation of PK

Descriptive statistics (n, mean, SD, CV% mean, geometric mean, CV% geo-mean, median, minimum and maximum) will be presented for all PK parameters (except Tmax and Tlast) by treatment. Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a non-parametric method, only n, median, minimum and maximum will be presented for this parameter. Any missing pharmacokinetic parameter data will not be imputed. [Table 3-8](#) summarizes the PK parameters and the planned descriptive statistics.

Summary statistics will be presented for PDR001 serum concentrations at each scheduled time point. Median concentration versus time profiles will be generated. Descriptive graphical plots of individual serum concentration versus time profiles will be generated in the final CSR.

The PK analyses will use the actual dose received for each particular PK profile. Parameters relating to the PK profile (e.g. AUC and Cmax) will be summarized for data collected in Cycle 1 and Cycle 3.

Table 3-8 PK parameters – descriptive statistics

Parameters	Descriptive statistics
Cmax, AUC _(0-Tlast) (AUCtau if available or with alternate dosing regimen), and Racc (modified for alternate dosing regimen)	n, mean, SD, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum.
Tmax, Tlast	Median, minimum, and maximum.
CV% mean = coefficient of variation (%) = $100 \cdot \text{sd} / \text{mean}$ CV% geo-mean = $\text{sqrt}(\text{exp}(\text{variance for log transformed data}) - 1) \cdot 100$	

Listings for PK parameters will be presented.

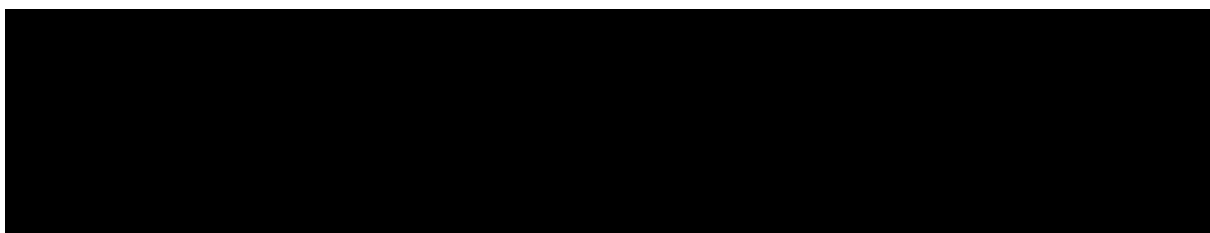
The pharmacokinetic analysis set will be used for the PK analysis, tables and listings. Refer to Novartis Guidance on Pharmacokinetic Data Analysis and Reporting for other details. Pharmacogenetics/pharmacogenomics is not conducted in this study.

Dose proportionality

The analysis of dose proportionality will be conducted for AUC_{tau} and C_{max} of PDR001 using a power model on log-transformed scale. The log-transformed PK parameters will each be regressed onto a fixed factor for log (dose). The 90% confidence interval (CI) of the slope for each PK parameter will be computed from the model and presented in a summary table.

3.7 Biomarkers

3.7.1 Introduction



There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

3.7.2 Biomarkers and purpose of analysis

Table 3-10 Biomarkers and purpose of analysis

Biomarker	Purpose of analysis
A large black rectangular redaction box covering the majority of the table's content.	
Systemic expression of immune-related markers (e.g. IFN- γ), anti-PDR001 antibodies	Characterize the systemic immune-cell population composition and immune-response at baseline and on treatment

3.7.3 Biomarker data

The Full Analysis Set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data. Assessment of associations between biomarker and safety data will be conducted using the Safety Set.

All subjects with evaluable PD measurements during phase I/II will be included in the data analysis, unless specified otherwise. Missing values will not be entered and will not be included in the analysis.

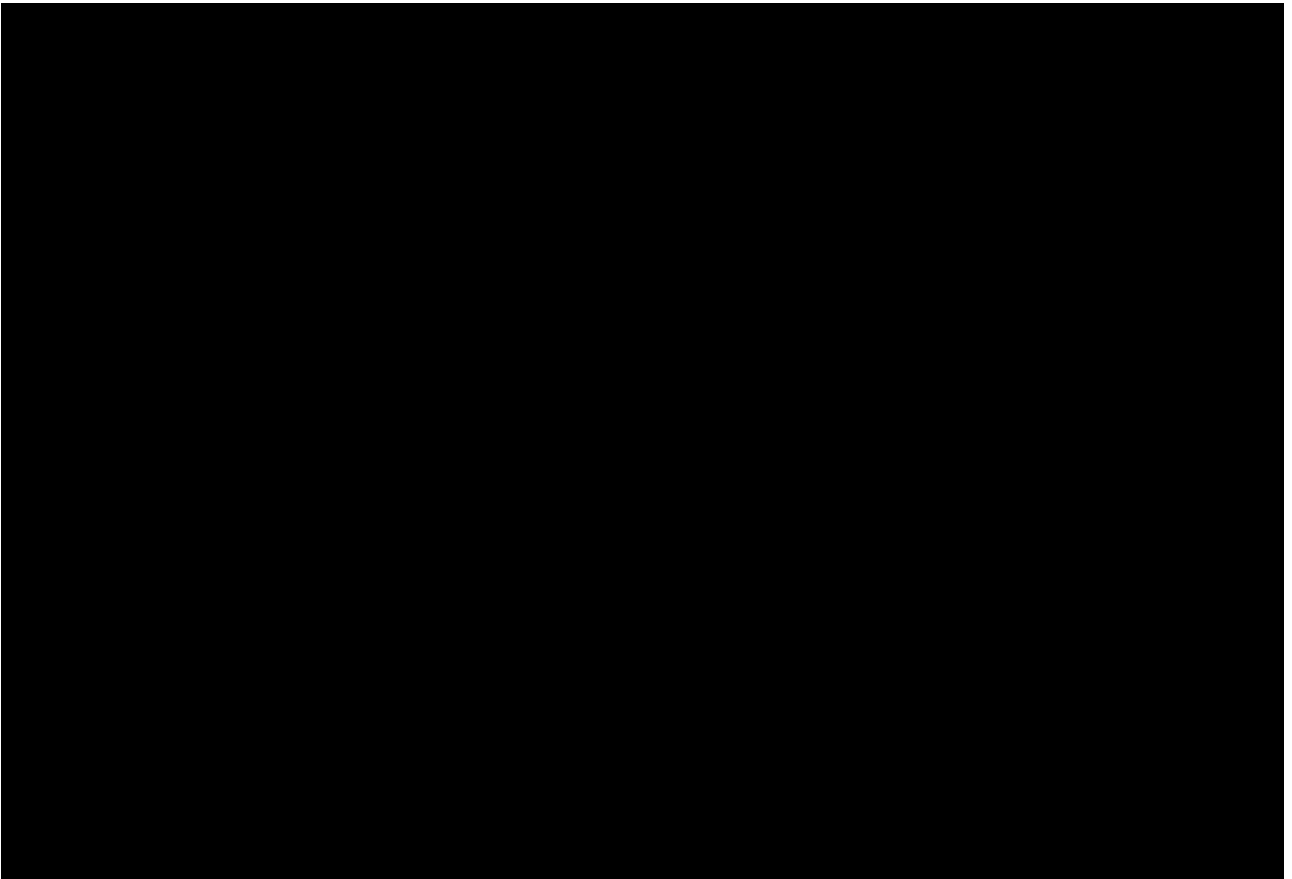
Table 3-11 Sample biomarker summary table

Biomarker	Time point	Sample	Method
BRAF V600 (melanoma and anaplastic thyroid cancer),	At molecular pre-screening (if needed) or Screening	Archival tumor sample OR newly obtained pre-treatment tumor biopsy	Immunohistochemistry
EGFR and/or ALK (NSCLC)	At molecular pre-screening (if needed) or Screening	Archival tumor sample OR newly obtained pre-treatment tumor biopsy	Immunohistochemistry
Cytokines	C1D1 Pre-dose C1D15	Plasma	Immunoassay

Biomarker	Time point	Sample	Method
	C3D1 Pre-dose 150 days after last dose		

3.7.3.1 General data handling and preprocessing

The pre-dose assessment that is closest to the first dose of study treatment will be used as the baseline value. For assessments performed in tumor biopsies, fresh biopsy results will be used for baseline when both archived and fresh tumor samples are available. When more than one biomarker assay results are available for a subject at baseline (e.g. archival and freshly obtained sample), the highest quality assay results collected the closest prior to treatment start will be used. If there are multiple assay results of the same highest quality at baseline, the mean of the assay results will be used for all statistical analyses. For any other time point, if replicate assay results exist from the same time point, the mean of the replicate values will be used for all statistical analyses.



3.7.5 Biomarker data analysis

3.7.5.1 Categorization of continuous biomarker data

New categorical variables will be derived from continuous percent positivity using predefined thresholds, if available. In addition to the predefined threshold, other thresholds may be established by exploring the data collected within the current trial itself. If the pre-defined thresholds are not available, new categorical variables will be derived for biomarkers using the median levels as the threshold. Alternatively, multiple thresholds may be evaluated in an exploratory fashion and an optimized cut-point will be chosen to provide the most optimal separation for the efficacy outcome between patients below and above the cut-off.

Table 3-12 listed the selected threshold for biomarker expression levels of some IHC biomarkers.

Table 3-12 Predefined threshold for some IHC biomarker expression levels

Analyte	Parameter	Categories
PD-L1	Percent positive tumor	<ul style="list-style-type: none"> Three-level category: 0 - < 1%; 1 - < 50%, ≥ 50% Two-level category: 0 - < 1% (PD-L1-); ≥ 1% (PD-L1+)
CD8	Percent marker area	<ul style="list-style-type: none"> Two-level category: 0 - < 1% (CD8 low); ≥ 1% (CD8 high)

3.7.5.2 Descriptive statistics for biomarker

The biomarker data will be listed for each subject for all time points and ordered by the treatment group. For each measurement, the mean, standard deviation, median, minimum, maximum, and number for each treatment group at each time point will be reported.

If repeated biomarker assessments are made at multiple visits e.g. pre and post treatment, absolute and relative change (percent change) from baseline will be calculated for each subject and reported by treatment group. If there are post-baseline data available, longitudinal plots showing mean changes may be generated only if post-baseline data for at least 3 patients in the same treatment group are available.

Counts (and percentages) by categories defined by the predefined thresholds will be reported at each time point and treatment group.

Furthermore, the following specifies the examples of outputs that will be produced to incorporate multiple biomarker types:

- [REDACTED]
- The expression levels of PD markers, including systemic cytokines, [REDACTED] at each time point and change from baseline, will be listed by patient and summarized (when sample size is sufficient) using descriptive statistics by treatment group.
- [REDACTED]

at each time point and change from baseline will be listed by patient and summarized (when sample size is sufficient) using descriptive statistics by treatment group.

- The EGFR, ALK and BRAF tumor mutation statuses will be summarized using descriptive statistics by treatment group. If a subject provided written documentation of these tumor mutation statuses to enter the screening phase, the provided results will be used. If not, the tumor mutation statuses from the molecular pre-screening assessment will be used. [REDACTED]

3.7.5.3 Association between biomarkers and clinical outcome

PD-L1 and potential predictors of efficacy

Associations of PD-L1 expression and efficacy outcome (e.g. ORR, DOR and DCR) will be assessed using various approaches, such as tabulations of ORR by PD-L1 expression status, Kaplan-Meier plots and estimates of PFS by PD-L1 expression status, [REDACTED] and OS estimates by PD-L1 expression status.

[REDACTED]

3.8 PD and PK/PD analyses

3.8.1 Immunogenicity

3.8.1.1 Sample ADA Status

Each IG sample is assessed in a three tiered anti-drug anti-body (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not subject to a confirmatory assay. Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples identified as positive in the confirmatory assay are considered ADA positive and are further characterized in the neutralization assay to indicate the presence of neutralizing antibodies (NAb). Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data:

- Result of assay according to pre-specified confirmatory cut point: ADA positive (yes) or ADA negative (no)
- Titer (for positive samples): numerical representation of the magnitude of ADA response
- Presence of NAb (for positive samples, if NAb assay results are available): yes or no
- Drug tolerance level: highest drug concentration that does not interfere in the ADA detection method
- Fold titer change (i.e. x-fold): threshold for determining treatment boosted

Sample ADA status is determined based on the following definitions:

- *ADA-inconclusive sample*: Sample where assay is ADA negative and PDR001 PK concentration at the time of IG sample collection is greater than or equal to the drug tolerance level or missing.
- *Unevaluable sample*: Sample where assay is not available.
- *Determinant sample*: Sample that is neither ADA-inconclusive nor unevaluable.

The following definitions apply only to determinant samples:

- *ADA-negative sample*: Determinant sample where assay is ADA negative and PDR001 PK concentration at the time of IG sample collection is less than the drug tolerance level.
- *ADA-positive sample*: Determinant sample where assay is ADA positive.
- *ADA-positive NAb sample*: Determinant sample where assay is ADA positive and presence of NAb = yes.

The following definitions apply only to post-baseline ADA-positive samples with a corresponding determinant baseline sample. To be classified as *treatment-boosted* or *treatment-unaffected*, both the post-baseline and baseline titer must be non-missing:

- *treatment-induced ADA-positive sample*: ADA-positive sample post-baseline with ADA-negative sample at baseline.
- *treatment-boosted ADA-positive sample*: ADA-positive sample post-baseline with titer that is at least *the fold titer change* greater than the ADA-positive baseline titer.
- *treatment-unaffected ADA-positive sample*: ADA-positive sample post-baseline with titer that is less than *the fold titer change* greater than the ADA-positive baseline titer.

NOTE: PK concentrations which are flagged for exclusion will still be used to determine ADA-inconclusive and ADA-negative samples. However, the PK concentrations that are out of long term stability will be excluded from any IG analyses.

The following summaries of ADA sample status (n and %) will be provided using *Immunogenicity prevalence set*:

- ADA-positive samples (i.e. ADA prevalence) and ADA-positive NAb samples, both overall and by time point (including baseline). For summaries by time point, the denominator is the number of subjects at that time point with a determinant sample.

Listings will be provided of sample ADA status (including titer for positive samples).

3.8.1.2 Subject ADA status

Any IG sample collected after 150 days of the last dose of PDR001 will not be used for summaries or derivations and will only be included in the listing.

Subject ADA status is defined as follows:

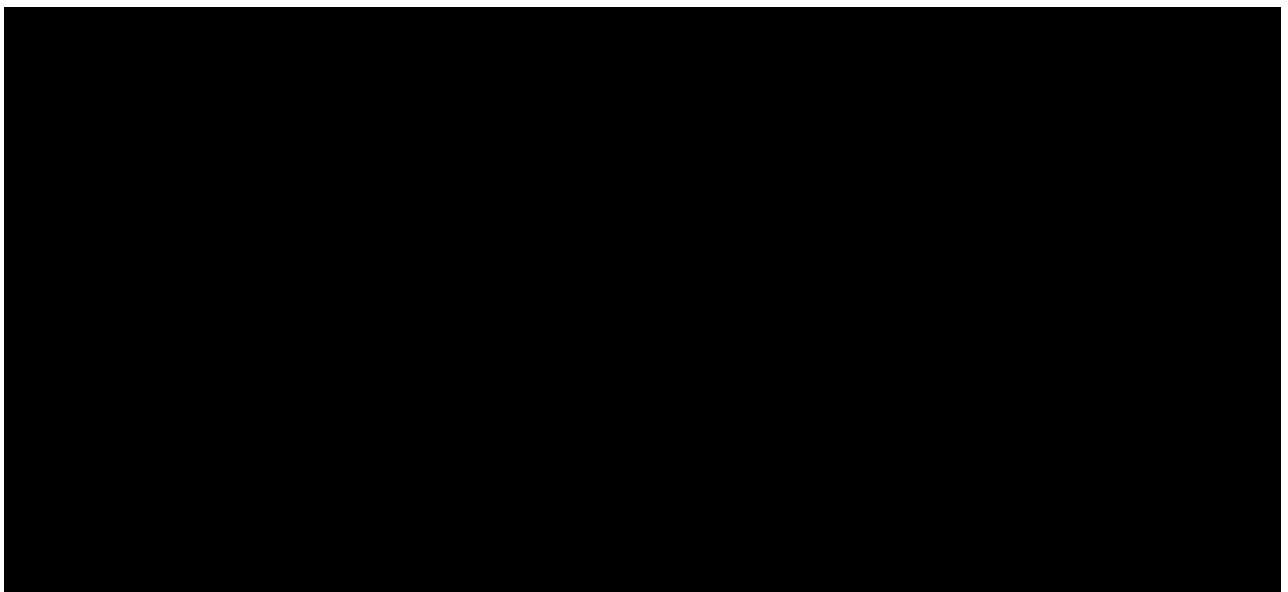
- *Treatment-induced ADA-positive subject*: subject with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- *Treatment-boosted ADA-positive subject*: subject with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.

- *Treatment-unaffected ADA-positive subject*: subject with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample.
- *Treatment-reduced ADA-positive subject*: subject with ADA-positive sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *ADA-negative subject*: subject with ADA-negative sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- *Inconclusive subject*: subject who does not qualify as treatment-induced ADA-positive, treatment-boosted ADA-positive, treatment-unaffected ADA-positive, treatment-reduced ADA-positive, or ADA-negative.

The following summaries of ADA subject status (n and %) will be provided using *Immunogenicity incidence set*:

- Treatment-boosted ADA-positive subjects; denominator is the number of subjects with ADA-positive sample at baseline.
- Treatment-induced ADA-positive subjects; denominator is the number of subjects with ADA-negative sample at baseline.
- ADA-negative subjects: denominator is the number of subjects in *Immunogenicity incidence set*.
- ADA-positive subjects (i.e. ADA incidence): calculated as the number of treatment-boosted ADA-positive and treatment-induced ADA-positive subjects; denominator is the number of subjects in *Immunogenicity incidence set*.

Listings will be provided of subject ADA status.



4 Appendix

4.1 Imputation rules

4.1.1 AE, ConMeds and safety assessment date imputation

Table 4-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	<ul style="list-style-type: none"> No imputation will be done for completely missing dates
day, month	<ul style="list-style-type: none"> If available year = year of study treatment start date then <ul style="list-style-type: none"> If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY Else set start date = study treatment start date. If available year > year of study treatment start date then 01JanYYYY If available year < year of study treatment start date then 01JulYYYY
day	<ul style="list-style-type: none"> If available month and year = month and year of study treatment start date then <ul style="list-style-type: none"> If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYYY. Else set start date = study treatment start date. If available month and year > month and year of study treatment start date then 01MONYYYYY If available month and year < month year of study treatment start date then 15MONYYYYY

Any AEs and CMs with partial/missing dates will be displayed as such in the data listings. Any AEs and CMs which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided. No imputation will be performed for AEs and CMs end dates.

4.1.2 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, and if the overall response at that assessment is CR/PR/SD/UNK, this/these incomplete date(s) are

not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan). Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. 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 previous and following assessment are not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date, then the evaluation is considered post-cut-off date and will be excluded from analysis.

Prior anti-neoplastic therapy

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used except it is set to be study treatment start date – 1 if available year = year of study treatment start date and stop date is not a full date or not earlier than study treatment start date or if available month and year = month and year of study treatment start date and stop date is not a full date or not earlier than study treatment start date.

End date:

Imputed date = min (start date of study treatment, last day of the month), if day is missing;

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Missing death date

For cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then impute max [(1 mmm-yyyy), min (last contact date + 1, cut-off date)].
- If both day and month are missing, then impute max [(1 Jan-yyyy, min (last contact date + 1, cut-off date)].

4.2 Definition and derivation rules for irRC

4.2.1 Total measurable disease burden

In irRC target and new measurable lesions are used to evaluate total measurable tumor burden (TMTB). TMTB is the sum of diameters (SOD) of all target and new measurable lesions. Similar to RECIST v1.1 where SOD of the target lesions is used for determination of target lesion response, for irRC TMTB is used for determination of target and new measurable lesion response.

4.2.1.1 Best percentage change from baseline in TMTB

Best percentage change from baseline in TMTB is defined as the percentage change from baseline to the smallest measured post-baseline TMTB occurring at or before the time of confirmed irPD.

4.2.2 Assessment of disease progression

To facilitate analysis, each assessment of progression is categorized as one of three types: pseudo progression, confirmed progression and unconfirmed progression.

4.2.2.1 Pseudo-progression

Subjects with a single irPD, followed by an assessment of irSD or better will be considered to have a pseudo-progression (pPD). For the purposes of analysis, pseudo-progressions are not treated as progression events.

4.2.2.2 Confirmed progression

Confirmed progression 1 (type 1, cPD1) is declared if a subject has 2 consecutive tumor assessments at least 4 weeks (28 days) apart both showing disease progression. Assessments with an UNK response or PD assessments < 28 days after initial PD, are discarded.

The first PD is flagged as cPD1 while all subsequent PDs are flagged as xPD1.

The table below shows two hypothetical data scenarios and programming instructions.

Sequence of assessments	Instructions
1 irPD 2 irUNK 3 irPD (Assessment 1 + 30 days)	<ul style="list-style-type: none"> • Assessment 3 is ≥ 28 days after Assessment 1 • Assessment 3 represents confirmation of irPD at assessment 1 • Assessment 1 irPD is flagged cPD1 • Assessment 3 irPD is flagged xPD1
1 irSD 2 irPD 3 irPD (Assessment 2 + 20 days) 4 irPD (Assessment 2 + 30 days)	<ul style="list-style-type: none"> • Assessment 3 is < 28 days after Assessment 2 • Assessment 4 is ≥ 28 days after Assessment 2 • Assessment 4 represents confirmation of irPD at assessment 2 • Assessment 2 irPD is flagged cPD1 • Assessment 3 and 4 irPDs are flagged xPD1

Confirmed progression 2 (type 2, cPD2) is declared if a subject discontinues treatment following a single PD with no subsequent assessments ≥ 28 days later. Assessments with an UNK response or PD assessments < 4 weeks (28 days) after initial PD, are discarded. Discontinuation of treatment is obtained from EOT case report form.

The assessment is flagged as cPD2 and subsequent PDs (< 28 days after first PD) are flagged as xPD2.

The table below shows two hypothetical data scenarios and programming instructions.

Sequence of assessments	Instructions
1 irSD 2 irPD - EOT	<ul style="list-style-type: none"> Subject withdraws after initial progression (Assessment 2) without confirmation Assessment 2 irPD is flagged as cPD2
1 irPD 2 irPD (Assessment 1 + 20 days) - EOT	<ul style="list-style-type: none"> Assessment 2 irPD is < 28 days after Assessment 1, so does not represent confirmation However, subject has completed treatment Assessment 1 irPD is flagged cPD2 Assessment 2 irPD is flagged xPD2

4.2.2.3 Unconfirmed progression

Subjects with a single irPD, and no assessment of irSD or better (assessment with an irUNK response or irPD assessments < 4 weeks after initial irPD, are discarded) continuing treatment at the time of the analysis will be considered as unconfirmed (uPD).

4.2.3 Best overall response

Assessment of BOR will be based on all assessments up to and including the first assessment of irPD (cPD1, cPD2, or uPD). Assessments made after start of new anti-cancer therapy, will be excluded.

BOR will be defined with the following hierarchy:

- irCR Two consecutive determinations of irCR ≥ 28 days (4 weeks) apart
Non-consecutive assessments of irCR may also result in BOR of irCR if all intervening assessments are irUNK
- irPR Two determinations of irPR (or better) ≥ 28 days (4 weeks) apart
The two determinations of irPR (or better) may be separated by one or more assessments of irSD, but may not be separated by an assessment of irPD
- irSD At least one irSD assessment (or better) > 42 days (6 weeks) after first treatment
- irPD Event flagged as cPD1, cPD2 or uPD ≤ 84 days (12 weeks) after first treatment
- irUNK All other cases

4.2.4 Time to event analyses:

4.2.4.1 Progression events

PDs flagged as pPD are not included in time to event analyses.

Subjects are classified as follows:

0	No event (censored)
1	Confirmed PD (cPD1 or cPD2)
2	Unconfirmed PD (uPD)

For the primary analysis of time to event endpoints, both confirmed and unconfirmed progression will be included as progression events with date of progression being the date of the assessment flagged as cPD1, cPD2 or uPD according to the algorithm defined in [Section 4.2.2](#).

A sensitivity analysis of time to event endpoints may be conducted in which subjects with unconfirmed PD are treated as censored, with date of last adequate assessment = visit date for assessment flagged uPD.

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

Assessment date

Assessment date is defined as for RECIST v1.1 ([\[CPDR001X2101 Amendment 8 Appendix 14.1.3.2.7\]](#)).

Start date

Start date is as defined for RECIST v1.1 ([\[CPDR001X2101 Amendment 8 Appendix 14.1.3.2.7\]](#)).

End dates for time to event variables

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 death as recorded on death eCRF
- Date of progression as defined in [Section 4.2.4.1](#).
- 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 progression 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 start of treatment is used.

Note: for sensitivity analyses of time to event endpoints ongoing Subjects with an unconfirmed progression may be censored at time of last assessment.

4.2.4.3 Censoring reason

Censoring reason is derived as for RECIST v1.1 ([Table 4-2](#)).

4.2.4.4 Duration of response

Duration of response is defined as a time interval between the first date of confirmed PR/CR and the date of progression as defined in [Section 4.2.4.1](#), or death due to any cause. Intervening assessments of pPD are excluded from the assessment.

Date of confirmed response

Response (irPR or irCR) should be confirmed by a second assessment no less than 4 weeks after the first assessment showing response. Date of response is then the date of the first of these two assessments. For confirmation of irCR the two assessments must be consecutive (intervening assessments of irUNK are permissible). For confirmation of irPR the two assessments do not need to be consecutive, but must not be separated by a pseudo-progression event.

The table below shows a hypothetical data scenarios with programming instructions.

Sequence of assessments	Instructions
1 irPR 2 irPD 3 irPR 4 irPR	<ul style="list-style-type: none"> The first PR (assessment 1) is followed by a pseudo-progression (assessment 2) and is therefore not confirmed Subsequently the Subject has a irPR (assessment 3) which is confirmed at the following assessment (assessment 4) The BOR for this Subject is irPR, with date of confirmed irPR equal to the date of assessment 3

4.3 Event dates used in PFS and DOR

Based on definitions outlined in [\[CPDR001X2101 Amendment 8 Section 14.1.3.2.9\]](#), the following analyses can be considered:

Table 4-2 Options for event dates used in PFS and DOR

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
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment ² (2) Date of next scheduled assessment ² (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

Situation	Options for end-date (progression or censoring) ¹ (1) = default unless specified differently in the protocol or RAP	Outcome
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1. =Definitions can be found in [\[CPDR001X2101 Amendment 8 Section 14.1.3.2.7\]](#)
2. =After the last adequate tumor assessment. “Date of next scheduled assessment” is defined [\[CPDR001X2101 Amendment 8 Section 14.1.3.2.7\]](#).
3. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

5 References

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