NOVARTIS

Clinical Development

PDR001/ Spartalizumab

CPDR001X2201 / NCT02605967

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

Statistical Analysis Plan (SAP)

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Version	Date	Changes
1.0	16-Feb-2021	First version of the SAP for the final CSR
2.0	23-Mar-2021	Updates implemented for the final CSR

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1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CPDR001X2201 that will be presented in the final 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 variable and datasets can be found in the Programming Datasets Specifications (PDS) document.

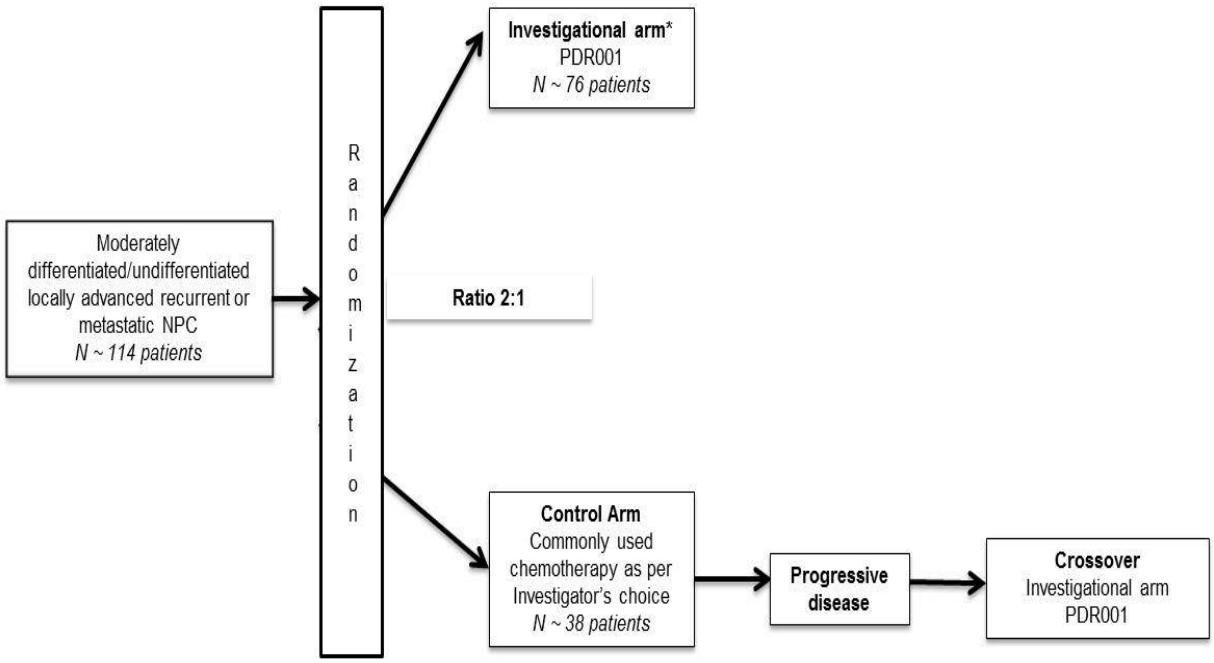
All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells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

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, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

1.1 Study design

This is an open-label, multi-center, randomized, controlled phase II study to evaluate the efficacy and safety of PDR001 versus investigator's choice of treatment in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic NPC who progressed on or after first-line treatment. Approximately 114 patients will be randomized with a 2:1 randomization ratio of investigational arm (PDR001) vs. control arm (chemotherapy). The randomization will be stratified by disease status (locally advanced recurrent NPC vs. metastatic NPC). Patients in the control arm will be allowed to crossover to PDR001 treatment if they have radiological progression (per RECIST v1.1) documented by an independent central review and discussed with Novartis. The study design is summarized in Figure 1-1.

Figure 1-1 Study Design



*Patients treated with PDR001 will continue treatment until confirmed PD as per irRC.

1.2 Study 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		
To assess the efficacy of PDR001 versus investigator's choice of chemotherapy in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic NPC who progressed on or after first-line therapy	Progression free survival (PFS) as per RECIST v1.1 using central assessment	Section 2.6
Secondary		
To evaluate the anti-tumor activity of PDR001 versus investigator 'choice of chemotherapy in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic NPC who progressed on or after first-line therapy	Overall survival (OS), overall response rate (ORR), duration of response (DOR), time to progression (TTP) and immune related progression free survival (irPFS) as per irRC using central assessment	Section 2.7
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)	Section 2.8

Objective	Endpoint	Analysis
To characterize the pharmacokinetic profile of PDR001 (patients in PDR001 arm)	Serum PK parameters (e.g. AUC, Cmax, Tmax, half-life); Serum concentration vs. time profiles	Section 2.9
To assess emergence of anti-PDR001 antibodies following one or more intravenous (i.v.) infusions of PDR001 (patients in PDR001 arm)	Presence and/or concentration of anti-PDR001 antibodies	Section 2.10
To assess potential predictive markers of efficacy of PDR001 in tumor sample (patients in PDR001 arm)	Assess potential associations between expression of PD-L1, CD8, Foxp3 and other immunological markers such as Lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin domain and mucin domain-3 (TIM-3), with anti-tumor activity	Section 2.10
To assess the pharmacodynamic effect of PDR001 in tumor sample (patients in PDR001 arm)	TIL counts and expression of immune-related genes (RNA/protein in tumor sample)	Section 2.10
To assess the pharmacodynamic effect of PDR001 in peripheral blood (patients in PDR001 arm)	Assess peripheral, soluble ligands and cytokine levels (including but not limited to IFN-γ, TNF-α, IL-6)	Section 2.10
[redacted]		

2 Statistical Methods

2.1 Data analysis general information

The data will be analyzed by Novartis personnel and/or designated CRO(s) using the most updated version of SAS, R and JAGS. PK parameters will be calculated using non-compartmental methods available in most updated version of Phoenix WinNonlin.

Data from participating centers in this study protocol will be combined, so that an adequate number of patients will be 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 (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

Data will be summarized and listed by study arms or by study treatment groups. Details are specified in each of the subsections.

Study arms refer to

- PDR001
- Chemotherapy

Study treatment groups refer to

- PDR001
- Chemotherapy
- Crossover

Crossover treatment group consists of the patients in the chemotherapy arm who crossover to PDR001 and treated with PDR001 after progression to chemotherapy. The clinical data collected before the crossover will be summarized in the chemotherapy treatment group; the clinical data collected after the crossover will be summarized or listed as appropriate in crossover treatment group.

2.1.1 General definitions

Study drug and study treatment

Study drug refers to PDR001. Study treatment refers to both PDR001 and Chemotherapy. Chemotherapy used in control arm may differ across centers.

Date of first/last administration of study drug and study treatment

The date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of study treatment was administered and recorded on the Dosage Administration Record (DAR) eCRF. For the sake of simplicity, the date of first (last) administration of study treatment will also be referred as start (last) date of study treatment.

Study day

For PDR001 and Chemotherapy treatment group:

The study day for safety assessments/events will be calculated using the start date of study treatment as reference. The study day for efficacy assessments/events will be calculated using the date of randomization as reference.

For safety assessments/events occurring on or after the start date of study treatment, study day will be calculated as:

Study day (days) = Event date – Start date of study treatment + 1

Therefore, the first day of study treatment is study day 1.

For safety assessment/events occurring prior to the start of the study treatment, study day will be negative and will be calculated as:

Study day (days) = Event date – Start date of study treatment

For efficacy assessments/events occurring on or after randomization, study day will be calculated as:

Study day (days) = Event date – Date of randomization + 1

For efficacy assessment/events occurring prior to randomization, study day will be negative and will be calculated as:

Study day (days) = Event date – Date of randomization

Study day will be displayed in the data listings.

For Crossover treatment group:

The study day for safety and efficacy assessments/events will be calculated using the start date of PDR001 treatment as reference.

For assessments/events occurring on or after the start date of PDR001 treatment, study day will be calculated as:

Study day (days) = Event date – Start date of PDR001 treatment + 1

Therefore, the first day of PDR001 treatment is study day 1.

For assessment/events occurring prior to the start of the PDR001 treatment, study day will be negative and will be calculated as:

Study day (days) = Event date – Start date of PDR001 treatment

On-treatment assessment/event

For PDR001 arm, an on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the start date of study treatment until the minimum date of (last date of study treatment + 30 days).

For crossover treatment group, an on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the start date of PDR001 treatment until the minimum date of (last date of study treatment + 30 days).

For chemotherapy arm, an on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the start date of study treatment until the minimum date of (the last date of study treatment + 30 days inclusive, start of crossover PDR treatment if crossovered).

2.2 Analysis sets

The number (%) of patients in each of the defined analysis set will be summarized using the FAS.

Full Analysis Set

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

Safety Set

The Safety Set includes all patients who received at least one dose of study medication and have at least one valid post-screening/post-baseline safety assessment. Patients will be analyzed according to the study treatment (regimen) they received.

The statement that a patient had no AEs (on the AE eCRF) constitutes a valid safety assessment. Patients will be classified according to treatment received, where treatment received is defined as:

- The treatment assigned if it was received at least once, or
- If the assigned treatment was never received, then the first treatment received when starting therapy with study treatment will be used for classification

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

Per-protocol Set

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

- Treatment according to the randomization scheme (see CPDR01X2201-Protocol-Section 6).
- Presence of at least one measurable lesion at screening/baseline according to RECIST v1.1 as per CPDR01X2201-Protocol-Appendix 1.
- At least 2 post-screening/post-baseline tumor assessments (unless disease progression is observed before that time).
- Have not been previously treated with PD-1- or PD-L1-directed therapy or any therapeutic cancer vaccine.

Patients will be classified according to treatment received.

In the final CRS no sensitivity analysis with PPS will be conducted.

Pharmacokinetic analysis set

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

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

Immunogenicity (IG) analysis set

The Immunogenicity prevalence set includes all subjects in the Safety 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 2.9.2 for the definition of determinant.

2.2.1 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. Details in Table 2-1.

Table 2-1 Protocol deviation and non-protocol deviation leading to exclusion from analysis set definitions

Analysis set	PDs leading to exclusion (ID)	Non-PDs leading to exclusion
FAS	No written inform consent (INCL01).	
Safety set	No written inform consent (INCL01).	No administration of study drug. No valid post-baseline safety assessment.
PPS	No written inform consent (INCL01). Receive study treatment not according to the randomization scheme (i.e., randomize to PDR but receive Chemotherapy, vice versa) (TRT01, TRT02) Patient has no measurable lesion as determined by RECIST 1.1 at baseline (INCL09) Have been previously treated with PD-1- or PD-L1-directed therapy or any therapeutic cancer vaccine. (INCL14)	No administration of study drug. Less than 2 post-screening/post-baseline tumor assessments (unless disease progression is observed before that time).
PAS	No written inform consent (INCL01).	No administration of study drug. No evaluable PK data.
Immunogenicity prevalence set	No written inform consent (INCL01).	No administration of study drug. No determinant IG sample at both baseline and post-baseline
Immunogenicity incidence set	No written inform consent (INCL01).	No administration of study drug No determinant IG sample at baseline or post-baseline or both

2.2.2 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.

2.2.3 Subgroup of interest

No subgroup analysis will be conducted in the final CSR as the primary efficacy analysis reported in the interim CSR was not statistically significant.

2.3 Patient disposition, demographics and other baseline characteristics

Summaries and listings described in this section will be done by study arms based on the FAS.

2.3.1 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. The following will be tabulated:

- Number (%) of patients who are still on-treatment (based on non-completion of the 'End of Treatment' page),
- Number (%) of patients who discontinued treatment (based on completion of the 'End of Treatment' page with discontinuation date and reason entered),
- Primary reasons for study treatment discontinuation (based on discontinuation reason entered in the 'End of Treatment' page),
- Number (%) of patients who discontinued from study (based on completion of the 'End of Post Treatment Phase Disposition' page with discontinuation date and reason entered),
- Primary reasons for study evaluation completion (based on discontinuation reason entered in the 'End of Post Treatment Phase Disposition' page).

2.3.2 Basic demographic and background data

Demographic data including age, sex, race, ethnicity, height, and baseline weight and ECOG(WHO) performance status will be listed and summarized. In addition, body mass index (BMI) and child bearing potential will be listed, and age (18-<65, 65-<85, ≥85 years) categories will be summarized.

BMI is calculated using the following formulas:

- BMI [kg/m2] = weight[kg] / (height[m]**2)

2.3.3 Medical History

Medical history and current (ongoing) medical conditions will not be reported in the final CSR.

2.3.4 Prior antineoplastic therapy

Prior anti-neoplastic therapy will will not be reported in the final CSR.

2.3.5 Diagnosis and extent of cancer

Diagnosis and extent of cancer (disease history) will not be reported in the final CSR.

2.4 Protocol deviations

Summaries and listings described in this section will be done by study arms based on the FAS.

The number (%) of patients with any 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 medication; other deviation). The full list of protocol deviations are documented in the Study Specification Document (SSD). COVID-19 specific protocol deviations will be listed. Details about COVID-19 impact are provided in Section 4.1.

2.5 Treatments (study treatment, rescue medication, other concomitant therapies, compliance)

Summaries and listings described in this section will be done by study treatment groups based on the Safety set. Exceptions are specified in each subsection.

2.5.1 Study treatment

Study treatment refers to:

- PDR001
- Chemotherapy: as per investigator's choice

Below summaries will be done for PDR001 treatment group. For chemotherapy, Duration of exposure (days) and Duration of dose interruptions (days) will be summarized, dosage administration records will be listed by patient and by each chemotherapy per investigator's choice. For patients in Chemotherapy arm who crossover to PDR001 after progression to chemotherapy, below summaries will be done as well for PDR001 treatment if there are more than 10 crossover patients.

Duration of exposure to PDR001 = (last date of exposure to PDR001) – (date of first administration of PDR001) + 1.

The last date of exposure to PDR001 is defined as: minimum date of (date of last administration of a non-zero dose of the PDR001 + 27 days, data cutoff date, death date);

Duration of exposure to Chemotherapy = (last date of exposure to Chemotherapy) – (date of first administration of Chemotherapy) + 1

The last date of exposure to Chemotherapy is defined in Table 2-2.

Table 2-2 Definition of last date of exposure to chemotherapy

Regimen	Definition of last date of exposure*
Daily administration of the study treatment, i.e., BID, QD and EVERY OTHER DAY	Date of last administration of a non-zero dose
study treatment with a cyclic administration: - WEEKLY (EVERY 7 DAYS) - 1 WEEK ON 3 WEEKS OFF - 21 DAYS ON 7 DAYS OFF - 2 WEEKS ON 1 WEEK OFF - 2 WEEKS ON 2 WEEKS OFF	The planned end date of the last cycle in which the last non-zero dose of the study treatment was administered: the date of first administration of study treatment in the last cycle + cycle length - 1 i.e., for 1 WEEK ON 3 WEEKS OFF, the cycle length is 28 days, last date of exposure = the date of first

- 2 WEEKS ON 3 WEEKS OFF - EVERY 2 WEEKS - EVERY 3 WEEKS - EVERY 4 WEEKS	administration of study treatment in the last cycle + 27 days; For EVERY 2 WEEKS, the cycle length is 14 days, last date of exposure = the date of first administration of study treatment in the last cycle + 13 days;

* If the derived last date of exposure goes beyond the data cutoff date, death date, then it should be truncated to the date of the minimum of (data cutoff date, death date).

Definitions of cumulative dose, actual dose intensity (DI), planned dose intensity (PDI), relative dose intensity (RDI), percentage of cycles dosed, percentage of cycles at the prescribed dose was received, as well as intermediate calculations, are as follows:

- Duration of dose interruptions (days): Sum of all dose delays. See definition of dose delay/interruption below.
- Cumulative dose (mg): sum of all doses of study drug taken by a patient
- Cumulative prescribed dose (*mg*): sum of all doses of study drug that was intended to have been taken during the treated period by a patient
- DI (mg/cycle): cumulative dose (mg)／number of doses scheduled per protocol during treatment period
- PDI (mg/cycle): cumulative prescribed dose (mg)／number of doses scheduled per protocol during treatment period
- RDI (%): 100 × DI (mg/cycle)／PDI (mg/cycle)

The duration of exposure to study treatment (including categories: <=4 weeks, 4-<=12 weeks, 12-<=16 weeks, 16-<=24 weeks and >24 weeks) will be summarized. In addition, the cumulative dose, DI, and RDI (including categories: <0.5, ≥0.5-<0.75, ≥0.75-<0.9, ≥0.9-<1.1, ≥1.1) will be summarized. The number (%) of patients who have dose interruptions and dose reductions, and the corresponding reasons, will be provided. The number of dose interruptions and dose reductions per patient and the duration of interruptions and dose reductions will be summarized.

All doses of the study treatment along with reasons for any dose change will be listed.

Dose interruption: 'Dose interrupted' field from the Dosage Administration CRF pages (DAR) will be used to determine the dose interruptions. For patients in Chemotherapy arm taking doublet or triplet chemotherapies, if 'Dose interrupted' field is ticked for all of the combo/triple components on the same day, then only count the dose interruption once.

2.5.2 Concomitant therapies

Concomitant therapies will not be reported in the final CSR.

2.5.3 Compliance

Compliance to the protocol will be assessed by the number and percentage of patients with protocol deviations. Details are provided in Section 2.4.

Compliance to the study treatment PDR001 will be assessed by the percentage of patients who took a predefined percentage (RDI categories: <0.5, 0.5-<0.75, 0.75- <0.9, 0.9-<1.1, ≥1.1) of the number of prescribed doses of study treatment. Details are provided in Section 2.5.1.

2.6 Analysis of the primary objective

2.6.1 Primary endpoint

The primary efficacy endpoint is progression-free survival (PFS) based on central review of tumor scan, as defined per RECIST v1.1 (CPDR01X2201-Protocol-Appendix 1).

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

2.6.2 Statistical hypothesis, model, and method of analysis

Patients are randomized in 2:1 ratio into either PDR001 arm or control arm. The primary efficacy endpoint, PFS as determined based on the central tumor assessment per RECIST v1.1, will be analyzed by study arm.

Kaplan-Meier plots will be provided in order to present PFS graphical outputs for the PDR001 and the control arm. KM estimates of the median and PFS rates at 2, 4, 6, 8 and 12 months will be given along with 95% confidence intervals. The FAS will be used for the primary analysis. In addition to the primary PFS analysis by study arm the KM estimates will be analyzed by PD-L1 and CD8 expression.

2.7 Analysis of the secondary efficacy variables

Evaluation of anti-tumor activity will be based on central review of overall lesion response according to RECIST v1.1 (see CPDR01X2201-Protocol-Appendix 1) and irRC (CPDR01X2201-Protocol-Appendix 2). The variables used to evaluate anti-tumor activity are OS, ORR, BOR, DOR, TTP as per RECIST v1.1 and irPFS as per irRC. Summaries and listings described in this section will be done by study arms based on the FAS.

Individual lesion measurements, overall lesion response, OS, DOR, and irPFS will be listed by patient. OS, ORR, BOR, DOR, TTP and irPFS will be summarized as per specification in Table 2-3. A waterfall plot of best percentage change from baseline in sum of longest diameters of target lesions per RECIST 1.1 and total measured tumor burden (TMTB) per irRC (CPDR01X2201-Protocol-Appendix 2) will be presented for each study treatment group.

Table 2-3 Analysis of the secondary efficacy variables

Endpoint	Definition	Analysis

OS	Time from the date of randomization to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.	A Kaplan-Meier plot for OS will be presented. Median OS (in months) with corresponding 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities (OS rate) with corresponding 95% CIs (Greenwood's formula, Kalbfleisch and Prentice 1980) at several time points (6, 12, 18 and 24 months) will be presented. The number (%) of deaths and patients censored will also be summarized.
irPFS (per irRC)	Time from the date of randomization to the date of the first documented disease progression (irPD) (CPDR01X2201-Protocol-Appendix 2), or death due to any cause.	Median irPFS (in months) with corresponding 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities (irPFS rate) with corresponding 95% CIs (Greenwood's formula, Kalbfleisch and Prentice 1980) at several time points (2, 4, 6, 8and 12 months) will be presented. The number (%) of progressions, deaths and patients censored will also be summarized. The analysis of irPFS will be done for PDR001 arm and crossover patients if there are more than 10 crossover patients.
TTP (per RECIST 1.1)	Time from date of randomization to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.	Median TTP (in months) with corresponding 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities (TTP rate) with corresponding 95% CIs (Greenwood's formula, Kalbfleisch and Prentice 1980) at several time points (2, 4, 6, 8 and 12 months) will be presented. The number (%) of progressions, deaths and patients censored will also be summarized.

BOR (per RECIST 1.1)	The best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence.	BOR will be summarized as observed proportion in each category, and corresponding 95% confidence intervals (CIs) based on the exact binomial distribution will be presented. Tumor volume best change from baseline of solid tumors will be presented graphically (waterfall graphs). Tumor assessments performed more than 30 days after the last study treatment (and before any new anti-neoplastic therapy) have to be considered in derivation of the BOR.
ORR (per RECIST 1.1)	Proportion of patients with a best overall response of confirmed CR or confirmed PR.	ORR and corresponding 95% confidence intervals (CIs) based on the exact binomial distribution will be presented.
DOR (per RECIST 1.1)	Time from the date of first documented response (confirmed CR or confirmed PR) to the date of the first documented disease progression or death due to underlying cancer.	Summaries of DOR will be provided if at least 10 patients responded to study treatment. Present DOR rate at 6, 10, 12, 18, 24 months.

2.8 Safety analysis

Summaries and listings described in this section will be done by study treatment groups based on the Safety set:

- PDR001
- Chemotherapy
- Crossover

For crossover treatment group, summaries will be done if there are more than 10 crossover patients.

The assessment of safety is based on the type and frequency of Adverse Events (AEs) as well as on the number of laboratory values that fall outside of pre-determined ranges (Common Toxicity Criteria for Adverse Events (CTCAE) grading limits or normal ranges as appropriate). Other safety data include electrocardiogram and vital signs.

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

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study treatment,
- On-treatment period: from day of first dose of study treatment to the end of safety follow up, i.e., for PDR001, to 30 days after last dose of PDR001; For chemotherapy, to 30 days after last dose of chemotherapy.

- Post-treatment period: starting at Day 31 after last dose of PDR001 for PDR001 treatment group; Starting at Day 31 after last dose of chemotherapy for chemotherapy treatment group.

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 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 treatment related adverse events will be collected. Select summaries of related adverse events will be produced for the combined on-treatment and post-treatment periods (Section 2.8.1).

2.8.1 Adverse events

AEs will be coded and graded using the latest version of MedDRA and CTCAE, respectively, available at the time of reporting. 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) will not be used in this study. Death information will be collected on the 'End of Treatment', 'Survival Information' and 'Death' eCRF pages.

AE Summaries (CSR outputs)

Primary AE summaries will include all AEs occurring 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 drug, 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 the PDR001 treatment group

The following AE summaries will be produced 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/or 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;

The following AE summaries will be produced for PDR001 for all AEs starting or worsening during the on-treatment or post-treatment periods:

- AEs suspected to be study treatment related;
- SAEs related to study treatment

The following listings will be produced:

- All adverse events (safety set)

Deaths (CSR Outputs)

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

All deaths will be listed for the safety set, deaths occurring after the treatment period will be flagged.

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. These summaries will include any events starting or worsening in the on-treatment period.

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.

Adverse events of special interests / 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

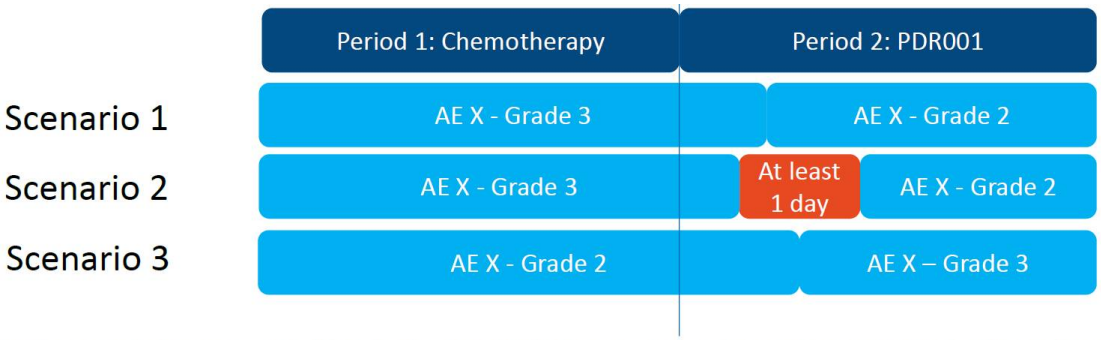
level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination 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 for treatment group PDR001 and Crossover. A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

Summarize adverse events in Crossover treatment group

Patients from randomized to Chemotherapy treatment group are allowed to crossover to PDR001 group after confirmation of PD to chemotherapy. Below diagram specifies how to summarize the AEs for crossover treatment group.



For Scenario 1: do not count AE X (Grade 2) in Period 2 (PDR treatment), as it is an AE starts in Period 1 (Chemotherapy) and resolving during Period 2;
For Scenario 2: count AE X (Grade 2) in Period 2, as this AE starts at least 1 day after previous AE, indicates it is a new AE starts in period 2, not a resolving previsous AE;
For Scenario 3: count AE X (Grade 3) in Period 2, as it is a worsening AE

2.8.2 Laboratory data

Laboratory data will be converted into SI units and classified (by Novartis statistical programming) into CTC grades according to CTCAE. Grade 5 will not be used.

A Grade 0 CTC grade will be set when laboratory value is:

- Within LLN and ULN and grading in both direction,
- Below ULN and grading in hyper direction,
- Above LLN and grading in hypo direction.

Laboratory data for which a CTC grading does not exist will be classified into low, normal, or high based on local laboratory normal ranges as applicable. For the laboratory parameters where the CTC grades depend on the normal ranges, when normal ranges are captured as 0 and 888888.xxx or above then the normal ranges and normal ranges indicator should not be present and the corresponding CTC grade should not be derived.

The following summaries will be produced for hematology and biochemistry parameters:

- For parameters with CTC grades: Shifts from baseline to the worst post-baseline CTC grade,
- For parameters with no CTC grades defined: Shifts from baseline to the worst post-baseline using low/normal/high classifications,

The following listings will be produced:

- Listing of patients with laboratory abnormalities of CTC grade 3 and 4

Table 2-4 and Table 2-5 list all laboratory parameters with CTCAE or normal ranges that have been collected in the study. The laboratory parameters that will be summarized in the CSR will be mentioned in the TLF shells document. Other labpratory parameters without confirmed normal ranges include:

EBV test, DNA levels in plasma: 'Copies/mL' will be reported units. EBV conversion factor: Copies/mL = 10^ log IU/mL / 0.369.

Serology exam of Anti-DNA antibodies (Abs), Anti-nuclear abs, Anti-phospholipid abs, Anti-mitochondrial abs.

Table 2-4 Laboratory parameters for which CTCAE grades are defined

Hematology and coagulation		**Biochemistry**	
White Blood Cells (WBC)	↑ ↓	Creatinine	↑
Hemoglobin	↓	Sodium	↑↓
Platelets counts	↓	Potassium	↑↓
Absolute Neutrophils	↓	Corrected Calcium	↑↓
Absolute Lymphocytes	↑ ↓	Magnesium	↑↓
APTT	↑	Albumin	↓
INR	↑	AST (SGOT)	↑
		ALT (SGPT)	↑
		Total Bilirubin	↑
		Inorganic Phosphate	↓
		Glucose (fasting)	↑↓
		Glucose, plasma (fasting)	↑↓
		Alkaline Phosphatase	↑

↑ Indicates that CTC grade increases as the parameter increases.
↓ Indicates that CTC grade increases as the parameter decreases.

Table 2-5 Laboratory parameters (without CTCAE grades) for which lab reference ranges are defined

Hematology and coagulation	Biochemistry	Serology
Prothrombin time (PT)	Blood urea nitrogen (BUN)	c-Reactive protein (CRP)
Absolute Basophils	Urea*	Rheumatoid factor (RF)
Absolute Eosinophils	TSH	
Absolute Monocytes	Total T4	
	Direct bilirubin	
	Indirect bilirubin	
	Calcium	
	Chloride	
	Bicarbonate	

*Urea will be converted to BUN and reported as BUN

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

xxx count = (WBC count) * (xxx %value / 100)

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

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [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.

2.8.3 Vital signs, weight and physical examinations

Vital sign parameters collected are systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and weight (kg). Vital sign values considered notably abnormal are defined in Table 2-6.

Table 2-6 Criteria for notable vital sign values

Vital sign	Criteria for clinically notable vital sign values
Systolic blood pressure [mmHg]	≥180 mmHg/≤90 mmHg with increase/decrease from baseline of ≥20 mmHg

Diastolic blood pressure [mmHg]	≥105 mmHg/≤50 mmHg with increase/decrease from baseline of ≥15 mmHg
Pulse rate [bpm]	≥100 bpm/≤50 bpm with increase/decrease from baseline of >25%
Body temperature [°C]	≥ 39.1
Weight [kg]	≥10% decrease/increase from baseline

The number and percentage of patients with notable vital sign valyes (high/low) will be presented by treatment group.

Patients with any clinically notable vital sign value will be listed.

2.8.4 Electrocardiograms

Baseline for ECG analysis is defined as the average of all available ECG measurements associated with the baseline assessment. Scheduled study day 1 pre-dose ECGs will be considered to have been obtained prior to study drug administration if dosing time is missing.

If a patient has more than one post-baseline measurement at a specific time point, the average of all available measurements associated with the nominal time point will be used for analyses (not when flagging abnormalities).

The following summaries will be provided for each applicable ECG parameter:

- Number (%) of patients having notable ECG values according to Table 2-7.

Table 2-7 Criteria for notable ECG values

ECG parameter	Criteria for notable ECG values
QT, QTcF	New absolute values >450 ms, >480 ms and >500 ms Change from baseline >30 ms and >60 ms
HR (bpm)	Increase from baseline >25% and value >100 bpm Decrease from baseline >25% and value <50 bpm
PR (ms)	Increase from baseline >25% and value >200 ms New PR >200 ms
QRS (ms)	Increase from baseline >25% and value >120 ms New QRS >120 ms

Patients with any notable change from baseline for each QT/QTc interval will be listed.

2.8.5 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of dose interruptions by study treatment. Reasons for dose interruption will be listed by patient and study treatment and summarized by study treatment. Cumulative dose, dose intensity and relative dose intensity of study treatment (see Section 2.5.1) will be also be used to assess tolerability.

2.9 Pharmacokinetic data

All PK analyses will be performed based on the PAS for PDR001 arm. Patient data may be removed on an individual basis. PK parameters will be calculated using noncompartmental methods and summarized as described in Table 2-8. The PK parameters considerd primary are AUCinf, AUCtau (AUC0-672h), AUClast, Cmax, and Tmax. Other PK parameters (CL, Vz, T1/2) are considered as secondary. All primary PK parameters will be summarized and all PK parameters will be listed.

The descriptive statistics of all pharmacokinetic parameters in the Table 2-8 for both Cycle 1 and Cycle 3 will include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum.

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

Table 2-8 PK parameters – descriptive statistics

Parameters	Descriptive statistics
AUCinf, AUCtau (AUC0-672h), AUClast, Cmax, Tmax, T1/2, Racc, CL, Vz, Clast, Tlast	Mean, standard deviation, CV% mean, geometric mean, CV% geometric mean, median, minimum and maximum
CV% = coefficient of variation (%) = sd/mean*100 CV% geometic mean = sqrt (exp (variance for log transformed data)-1)*100	

2.9.1 Data handling principles

Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

Missing concentration values will be reported as is in data listings. Concentration values below Lower limit of quantitation will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

2.9.2 Immunogenicity

The presence and/ titer of anti-PDR001 antibodies, at each scheduled time point, will be listed by patients. Overall immunogenicity may be summarized when sample size is sufficient.

2.9.2.1 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. 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
- 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.

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.

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

- ADA-positive samples (i.e. ADA prevalence), 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).

2.9.2.2 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.

2.10 Biomarkers

2.10.1 Introduction

As a project standard only biomarkers collected in the clinical database will be analyzed. [redacted]

[redacted]

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of blood / archival tumor samples / fresh tumor biopsies / fine needle aspirates due to either practical or strategic reasons (e.g. issues related to the quality and/or quantity of the samples or issues related to the assay). 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.

2.10.2 Outline of the data analysis

Additional analyses that may be performed after the completion of the final (end-of-study) CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

2.10.3 Biomarker objectives

The biomarker objectives and corresponding endpoints are described in Table 1-1.

2.10.4 Biomarker analysis data

The Full Analysis Set will be used for all biomarker analysis. All statistical analyses of biomarker data will be performed on patients treated with PDR001 with biomarker data. Table 2-9 listed the biomarker, collection time and purpose of analysis.

Table 2-9 Sample biomarker summary table

Biomarker	Timepoint	Sample	Purpose of analysis
Immune-related genes, including but not limited to PD-L1, CD8, LAG-3, and TIM-3	Screening/Baseline	Newly obtained or archival tumor sample	Assess potential predictive markers of efficacy of PDR001
Immune-related genes, including but not limited to PD-L1, CD8, and TIM-3	Anytime between C3D1 and End of Treatment	Newly obtained tumor sample	Assess the pharmacodynamic effect of PDR001 in tumor sample
Cytokine analysis markers, including but not limited to IFN-γ, TNF-α, IL-6	C1D1 (pre-dose) C1D8 C1D15 C2D1 (pre-dose) C2D8 C2D15 End of Treatment	Blood sample for plasma cytokine analysis	Assess the pharmacodynamic effect of PDR001 in peripheral blood

Biomarker	Timepoint	Sample	Purpose of analysis
[redacted]			

2.10.5 Data analysis of biomarkers

Basic analysis and reporting are specified in Table 2-10.

Percent change is calculated as ((visit i - baseline)/baseline)*100.

Fold change is calculated as visit i /baseline.

Table 2-10 Reporting of analysis

Biomarker	Report
Immune-related genes, including PD-L1, CD8, LAG-3 and TIM-3 from tumor sample	Listing of biomarkers, including demographic variables, collect time point, levels and clinical endpoints.
	Summary table: levels at each time point (baseline and post-baseline) and change/percent change/fold change from baseline at each time point. Descriptive statistics include N, mean, standard deviation, % CV, median, minimum and maximum. For fold change, geometric mean and geometric % CV will also be included.
	Summary tables: PFS will be summarized for subjects with a. PD-L1 high (PD-L1 >= 50%)/mid (PD-L1 1% - 50%)/low (PD-L1 < 1%) expression at baseline and b. CD8 < 1% CD8 ≥ 1% expression at baseline using the Kaplan-Meier (KM) method. Median PFS, with corresponding 90 CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for PFS proportions at specific timepoints, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided.
Cytokine analysis markers, including but not limited to IFN-γ, TNF-α, IL-6 from blood sample	Summary table: levels at each time point (baseline and post-baseline) and change/percent change/fold change from baseline at each time point. Descriptive statistics include N, mean, standard deviation, % CV, median, minimum and maximum. For fold change, geometric mean and geometric % CV will also be included.
	Listing of biomarkers, including demographic variables, collect time point, levels and clinical endpoints.

2.11 Patient reported outcomes

Not Applicable.

[redacted]

2.13 Interim analyses

No formal interim analyses are planned.

3 Sample size calculation

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

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

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

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

4 Change to protocol specified analyses

4.1 Planned analyses due to COVID-19

The COVID-19 pandemic had minimal impact on this study because at the start of the pandemic, the vast majority of subjects had discontinued the study treatment and completed the safety follow-up phase. COVID-19 specific protocol deviations will be listed.

5 Appendix

5.1 Baseline

For PDR001 and Chemotherapy arm:

For safety assessments/events, baseline is the last available and valid assessment performed or value measured within 28 days before the first administration of study treatment, unless otherwise stated under the related assessment section. For demographic data (including age, sex, race, ethnicity, height, baseline weight and ECOG performance status) baseline value outside the 28 days window may be reported as long as it is the last available and valid assessment performed or value measured before the first administration of study treatment . Baseline can be the day before first treatment administration or the same day as first treatment administration if a pre-dose assessment/value is available (e.g., ECG, PK samples, samples for biomarkers).

If time is recorded for the first treatment dose and for a specific assessment performed the day of first dose, this assessment will be 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 will be considered as baseline if, according to protocol, it should be performed before the first dose.

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

For efficacy assessments/events, baseline is the last available and valid assessment performed or value measured within 28 days before the date of randomization. If pre-randomization assessment is not available, assessment within 7 days after randomization can also be considered as baseline assessment.

For crossover treatment group:

For safety and efficacy assessments/events: baseline is the last available and valid assessment performed before PDR001 dosing.

5.2 Handling of missing and partial dates

AE, Conmeds and safety assessment data imputation

Table 5-1 Imputation of start dates (AE, CM)

Missing Element	**Rule**
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o 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	• If available month and year = month and year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  o Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

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.

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)].

Incomplete date of initial diagnosis of cancer, date of most recent recurrence and date of first recurrence/progression

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

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 that 'study treatment start date-1' should be used other than 'study treatment start date' when applicable in the imputationEnd date:

Imputed date = min (start date of study treatment-1, last day of the month), if day is missing;

Imputed date = min (start date of study treatment-1, 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.

For the patients who are randomized but never received study treatment, 'randomization date' should be used other than 'start date of study treatment' in the imputation.

New anti-neoplastic therapy

Start date:

- If Day is missing, then impute to the max (reference start date, first day of the month).
- Day and month are missing then impute to the max (reference start date, Jan 1).

- If Year, Month and Day are missing then impute to reference start date
- Reference start date will be last date of study drug + 1.

End date:

No imputation.

5.3 Construction of waterfall graphs

Waterfall graphs will be used to depict anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of target lesions for each patient per RECIST 1.1 and total measured tumor burden (TMTB) per irRC (CPDR01X2201-Protocol-Appendix 2).

Note: Patients without any valid assessments to calculate a percentage change from baseline value will be excluded from the graphs. Assessments with an unknown overall response will be included as long as the sum of diameters of target lesions is correctly computed on the same lesions assessed at baseline.

Patients will be ordered in the graph from left (worst change) to right (best change).

1. Bars above the horizontal axis (0%) representing tumor growth,

2. Bars under the horizontal axis (0%) representing tumor shrinkage.

The total number of patients displayed in the graph (n) over the total number of patients in the FAS (N) will be shown. The best overall response (BOR) will be displayed above each of the displayed bars in the graph. Symbols will be used to differentiate groups of interest, i.e. study treatment group. A horizontal threshold line at -30% may be shown. A heatmap may be added in order to display per patient (matching with the bar on the waterfall plot) the information regarding biomarker status. Details will be provided in TFL shells.

6 References

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