NOVARTIS

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

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
APC	Antigen Presenting Cell
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
[redacted]	[redacted]
CMO & PS	Chief Medical Office and Patient Safety
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
DCR	Disease Control Rate
DDP	Dose Determining Pharmacokinetic Set
DDS	Dose-Determining Safety Set
DLT	Dose Limiting Toxicity
DOR	Duration of Response
EBV	Epstein Barr Virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
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
[redacted]	[redacted]

[redacted]

mAb(s)	monoclonal Antibody(ies)
MHC	Major Histocompatibility Complex
MSI-High (MSI-H)	Microsatellite instability high
MTD	Maximum Tolerated Dose
NSCLC	Non-Small Cell Lung Carcinoma
NYHA	New York Heart Association
ORR	Overall Response Rate
[redacted]	[redacted]
PAS	Pharmacokinetic Analysis Set
[redacted]	[redacted]
PD	Pharmacodynamics
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS	Progression Free Survival
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Progesterone Receptor
RAP	Report and Analysis Plan
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
[redacted]	[redacted]
RP2D	Recommended phase 2 dose
SAE(s)	Serious Adverse Event(s)
SEB	Staphylococcal Enterotoxin B
SEC	Safety Event Categories
SJS	Stevens Johnson Syndrome
TCR	T Cell Receptor
TEN	Toxic Epidermal Necrolysis
[redacted]	[redacted]
[redacted]	[redacted]
TNBC	Triple Negative Breast Cancer

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: 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
Personal data	Subject information collected by the investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
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 from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Protocol summary:

Protocol number	CPDR001X2101
Title	Open label multicenter Phase I/II study of the safety and efficacy of PDR001 administered to patients with advanced malignancies.
Brief title	Phase I/II study of PDR001 in patients with advanced malignancies.
Sponsor and Clinical Phase	Novartis Phase I/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this "first-in-human" study of PDR001 is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of PDR001 administered i.v. as a single agent to adult patients with solid tumors By blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2, PDR001 inhibits the PD-1 immune checkpoint, resulting in activation of an antitumor immune response by activating effector T-cells and inhibiting regulatory T-cells.
Primary Objective(s)	Phase I: To estimate the RP2D and/or the MTD for PDR001 Phase II: To estimate the anti-tumor activity of PDR001
Secondary Objectives	● To characterize the safety and tolerability of PDR001 ● To characterize the pharmacokinetic profile of PDR001 ● To further investigate the anti-tumor activity of PDR001
Study design	This study has been designed as a phase I/II, multi-center, open-label study starting with a phase I dose escalation part followed by a phase II part. PDR001 will be administered every 2 weeks (or every 3 or 4 weeks) until patient experiences unacceptable toxicity, progressive disease per immune related Response Criteria (irRC) and/or treatment is discontinued at the discretion of the investigator or the patient.
Population	The phase I part of the study will be conducted in adult patients with advanced solid tumors. The phase II part of the study will be conducted in adult patients enrolled in four distinct diseases (melanoma, NSCLC, TNBC and anaplastic thyroid cancer)
Inclusion criteria	1. Written informed consent must be obtained prior to any screening procedures 2. Patient (male or female) ≥ 18 years of age 3. Phase I part: Patients with advanced/metastatic solid tumors, with measurable or non-measurable disease as determined by RECIST version 1.1 (refer to Appendix 1), who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists. 4. Phase II part: Patients with advanced/metastatic solid tumors, with at least one measurable lesion as determined by RECIST version 1.1, who have progressed following their last prior therapy, and fit into one of the following groups: ● Groups 1a and 1b: NSCLC ● Patients with NSCLC must have had disease recurrence or progression during or after no more than one prior systemic chemotherapy regimen (platinum doublet-based) for advanced or metastatic disease. Prior maintenance therapy is allowed (e.g. pemetrexed, erlotinib, bevacizumab). ● Only patients with EGFR mutation-negative tumor are eligible (defined as negative for exon 19 deletions and for the L858R mutation in EGFR at a minimum; however, if more extensive EGFR mutation testing has been performed, the tumor must not harbor any known activating EGFR mutations in Exons 18-21 in order to be considered EGFR mutation-negative). All patients must be tested for EGFR mutational status and, for ALK translocation status if no mutation is detected in EGFR. Patients with ALK translocation-positive NSCLC must have had disease progression following treatment with a corresponding inhibitor and no more than one systemic chemotherapy regimen (platinum doublet-based), in any sequence. ● Group 2: Melanoma ● All patients must have been tested for BRAF mutations. Patients with BRAF V600 mutation positive melanoma must have clinical or radiological evidence of

	disease progression during or after Treatment with a BRAF inhibitor (alone or in combination with other agents). Patients without BRAF mutation are not required to have received a prior therapy. ● Group 3: Triple negative breast cancer ● Group 4: Anaplastic thyroid cancer ● Patients are not required to have received or progressed on a prior therapy. ● Patients in this indication must not be at short term risk for life threatening complications (such as airway compromise or bleeding from locoregional or metastatic disease). ● Chemoradiation and/or surgery should be considered prior to study entry for those patients with locally advanced disease if those therapies are considered to be in the best interest of the patient. 5. ECOG Performance Status ≤ 1. 6. Patients must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy. Patient must be willing to undergo a new tumor biopsy at baseline or at molecular pre-screening if applicable, and during therapy on this study. For patients in the phase II part of the study, exceptions may be granted after documented discussion with Novartis. After a sufficient number of paired biopsies are collected, the decision may be taken to stop the collection of biopsies.
Exclusion criteria (selected)	1. History of severe hypersensitivity reactions to other mAbs 2. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. 3. History of drug-induced pneumonitis or current pneumonitis. 4. Active infection requiring systemic antibiotic therapy. 5. HIV infection. 6. Active HBV or HCV infection. 7. Patients with ocular melanoma. 8. Systemic anti-cancer therapy within 2 weeks of the first dose of study treatment. For cytotoxic agents that have major delayed toxicity, e.g. mitomycin C and nitrosoureas, 4 weeks washout period. For patients receiving anticancer immunotherapies such as CTLA-4 antagonists, 6 weeks is indicated as the washout period. 9. Prior PD-1- or PD-L1-directed therapy. 10. Patients requiring chronic treatment with systemic steroid therapy, other than replacement-dose steroids in the setting of adrenal insufficiency. Topical, inhaled, nasal and ophthalmic steroids are not prohibited. 11. Patients receiving systemic treatment with any immunosuppressive medication (other than steroids as described above). 12. Use of any live vaccines within 4 weeks of initiation of study treatment. 13. Presence of ≥ CTCAE grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if ≥ CTCAE grade 3) due to prior cancer therapy.
Investigational and reference therapy	PDR001
Efficacy assessments	Tumor assessment per RECIST v1.1 and per irRC
Safety assessments	Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs
Other assessments	Serum PK parameters, immunogenicity [redacted]. Pharmacodynamic assessment on pre- and post- treatment newly obtained tumor samples, plasma [redacted].
Data analysis	The study data will be analyzed and reported based on all patients' data of the Phase I and Phase II parts up to the time when all patients have completed at least six cycles of treatment or discontinued the study.
Key words	Phase I/II, PDR001, Checkpoint inhibitor, PD-1, PD-L1.

[redacted]

Amendment 08 (24-May-2019)

Amendment rationale

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

Study Status

The CPDR001X2101 study started enrollment on 27-Apr-2015. The last patient was enrolled on 22-Mar-2018. A total of 319 patients have been treated: 58 patients in the dose escalation part and 261 patients in Phase II part of study (118 in NSCLC groups, 61 in melanoma group, 40 in TNBC group and 42 in anaplastic thyroid cancer group). As of 06-May-2019, 25 patients were still on treatment.

Changes to the protocol

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

Section 4.3: Definition of end of study:

- Addition of language to account for patients who would transfer into another study or an alternative treatment option to continue provision of study treatment.

Section 7.1.4: Discontinuation of study treatment:

- Addition of language to specify that patients who transfer to another study or an alternative treatment option to continue provision of study treatment will complete end of treatment procedures.

Section 7.1.6: Follow up period:

- Addition of language to specify that patients who transfer into another study or an alternative treatment option to continue provision of study treatment will not complete the safety, disease progression and survival follow up.

IRBs/IECs

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

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

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

[redacted]

Amendment 07 (16-Jul-2018)

Amendment rationale

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

After the occurrence of a case of Stevens Johnson Syndrome in a study with PDR001 in combination with another investigational agent, the dose modification guidelines for protocols using PDR001 were updated to mandate permanent discontinuation of study treatment for patients who experience SJS or Lyell syndrome/toxic epidermal necrolysis (TEN). This change has already been implemented as part of an urgent safety measure released on 15 June 2018. This protocol amendment is now formalizing these changes in the table describing follow up evaluations for selected toxicities.

In addition, the protocol has been revised to align with recently published guidelines on the clinical management of suspected immune-related toxicities, the dose modification section of the protocol and corresponding table were updated. The Phase I part of the study has been completed, and therefore the DLT table will not be changed. As the dose modification table will be based on the most recent guidelines, reference to the events meeting the definition of a DLT after the DLT period and how to handle them has been removed.

Other changes to the protocol include:

- The exclusion criteria has been amended to remove the use of condom for male study participants receiving PDR001. Because monoclonal antibodies are not genotoxic due to their high molecular weight, and are not expected to interact with DNA. In addition, they have a low distribution to the semen, a relatively small volume of semen delivered to the partner, and very low absorption. Fetal harm from semen delivery is therefore biologically implausible and the amount of monoclonal antibodies able to gain access to the partner's systemic circulation via trans-epidermal transfer would be expected to be extremely low.
- [redacted]
- Update of language for irRC assessment to clarify criteria for new measurable lesions and irRC response in case of only non-measurable disease at baseline.
- The removal of the reporting of total dose per cycle from statistical section, given dose intensity and relative dose intensity already serve as metrics of study treatment. More details and clarifications were also added for reporting other secondary efficacy objectives. Moreover modification have been made to follow Novartis analysis standards safety.
- The withdrawal of consent language has been revised to differentiate sample use after a patient withdraws consent based on the different regulations/laws around the world.
- Further minor changes have been made to correct inconsistencies.

[redacted]

Study status

The CPDR001X2101 study started enrollment on 27-Apr-2015. The last patient was enrolled on 22-Mar-2018. A total of 319 patients have been treated. Fifty-eight patients have been treated in the dose escalation part and 261 patients have been treated in Phase II part of the study (118 in NSCLC groups, 61 in melanoma group, 40 in TNBC group and 42 in anaplastic thyroid cancer group).

Changes to the protocol

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

Section 3: Objectives and endpoints

- Clarification that ORR in Phase I and PFS, DOR and DCR in Phase I and Phase II part are per both RECIST 1.1 and irRC was made in Table 3-1

Section 5.3: Exclusion criteria

- The exclusion criterion 25 has been deleted to reflect that use of a condom is no longer required. Consequently pregnancy outcomes collection for the female partners of any males who took treatment in the study is not required anymore and has been removed in Section 8.3

Section 6.3.1: Dose modification and dose delay

- Instruction for dose modification was updated and Table 6-4 updated accordingly. The list of abbreviations was updated to add SJS and TEN

Section 7.1.4.1: Replacement policy

- Inconsistency in writing DDS across sections has been corrected.

Section 7.1.5: Withdrawal of consent

- Withdrawal of consent language was revised and changes regarding the use of samples after consent is withdrawn were implemented. Update was also implemented on Glossary

Section 7.2: Assessment types

- [redacted]
- Clarification that collection of central ECG (Section 7.2.2.6) and PK and IG samples (Section 7.2.3) will stop after the first primary CSR data cut-off as it was previously indicated as primary CSR only

Section 8.2: Serious adverse events

- Drug Safety and Epidemiology (DS&E) has been replaced by Chief Medical Office and Patient Safety (CMO & PS) in Section 8.2.2. Change has also been made in Section 8.3 and abbreviation added in list of abbreviations

Section 8.3: Pregnancies

- Follow-up of newborn has been extended from 3 months to 12 months

Section 10.1.5: Dose-determining pharmacokinetic set

[redacted]

- Clarification provided that DDP is on Phase I dose escalation part

Section 10.3: Treatments (study treatment, concomitant therapies, compliance)

- Total dose per cycle summary has been deleted as already covered by relative dose intensity summary.

Section 10.4.2: Statistical hypothesis, model, and method of analysis

- Paragraph on groups sample size has been updated to correct inconsistencies with other sections.

Section 10.5: Secondary objectives

- Update has been made to clarify data reporting for secondary efficacy objectives (Section 10.5.2) and safety objectives (Section 10.5.3.2). New references have been added to Section 13 (References).
- Removal or urinary test and frequency table for newly occurring on –treatment grades 3 or 4 as per current standard (Section 10.5.3.3).
- Description of analysis of Time To Response has been removed to align text with Table 3-1. The same was removed from List of abbreviations.

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

- Wording has been updated to provide further clarifications on irRC assessment and Table 14-6 updated accordingly

IRBs/IECs

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

The changes in this amendment identified above as being related to the USM have already been implemented by a USM letter issued on 15 June 2018. These changes are required for patient safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore they were required to have been implemented prior to IRB/IEC approval of this amendment.

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

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

Amendment 06 (27-Jul-2017)

Amendment rationale

The main purpose of this amendment is to remove the requirement for progression on prior therapy for patients with anaplastic thyroid cancer; patients are no longer required to have received therapy prior to being eligible for treatment with PDR001. Outcomes for patients with this disease are dismal with a median life expectancy after diagnosis of less than six months

[redacted]

(Neff et al2008). Given the poor outcome after standard therapy current NCCN treatment guidelines recommend that all patients be considered for clinical trials (Neff et al. 2008; NCCN Guidelines (version 2.2017): Thyroid Carcinoma).

Some data suggest that this disease may be sensitive to PD-1 blockade. In published data, six of eight tumors from patients with anaplastic thyroid cancer expressed high levels of PD-L1 on tumor cells and were infiltrated by lymphocytes (Bastman et al, 2016). In preliminary data from the first 12 anaplastic thyroid cancer patients treated and evaluable for efficacy in the phase II part of this ongoing study (CPDR001X2101), one patient has a confirmed partial response (~ -52% by RECIST criteria) and an additional patient has a confirmed reduction in their disease burden (~ -14% by RECIST criteria). However, because of the aggressive nature of the disease, most anaplastic thyroid cancer patients on the trial to date have developed progressive disease or died prior to the first scheduled imaging evaluation (at eight weeks), allowing little time for immunotherapy to provide benefit. The inclusion criteria are therefore revised in this amendment to allow treatment earlier in the disease course.

Specific changes to inclusion criterion #4 for patients with anaplastic thyroid cancer include:

1. Patients are not required to have received or progressed on a prior therapy.
2. Patients must not be at short term risk for life threatening complications (such as airway compromise or bleeding from locoregional or metastatic disease).
3. Chemoradiation and/or surgery should be considered prior to study entry for those patients with locally advanced disease if those therapies are considered to be in the best interest of the patient.

Other changes to this protocol include:

Mutations affecting BRAF occur in approximately 11% - 27% of patients with anaplastic thyroid cancer (Tiedje et al 2017; Guerra et al 2013; Kunstman et al 2015). To facilitate a more complete understanding of the patient population benefiting from treatment with PDR001, tumor samples will be tested to determine BRAF V600 mutational status. Knowledge of the BRAF mutation status is not required for study entry.

The available preclinical data and analysis of triplicate, centrally reviewed ECGs collected during the study indicate that PDR001 does not have a risk of QTc prolongation (PDR001 Investigator's Brochure Edition 6). This amendment will therefore require ECG collection only at Screening and as clinically indicated.

Prohibited concomitant therapy has been modified to better align with medical practice in immuno-oncology. Specifically, patients who experience RECIST progression in one location (such as in the brain) may nonetheless continue to receive clinical benefit from PDR001 treatment provided selective treatment of a site of metastasis was allowed (such as irradiation of brain metastases). Therefore, in the setting of RECIST progression, but where the investigator is of the opinion that the patient is experiencing clinical benefit, the amended protocol will allow radiotherapy and surgery.

The low prevalence of the anaplastic thyroid cancer may lead to uneven speed in recruitment across indications in phase II part. Therefore the data in different indications may mature at different times. Separate primary analyses and indication-specific complete clinical study

[redacted]

reports may be provided for this study. Therefore, the protocol has been amended to allow separate primary analyses.

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

[redacted]

Minor inconsistencies were corrected and clarifications made throughout the document.

Study status

The CPDR001X2101 study started enrollment on 27-Apr-2015. As of 29-Jun-2017, a total of 286 patients had been treated. Fifty-eight patients had been treated in the dose escalation part and 228 patients had been treated in Phase II part of the study (114 in NSCLC groups, 61 in melanoma group, 40 in TNBC group and 13 in anaplastic thyroid cancer group). Enrollment to the anaplastic thyroid cancer group in the Phase II part is ongoing.

Changes to the protocol

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

Section 4.1: Description of study design

- Replacement of description of data reporting with reference to section 10 where data reporting is described.

Section 5.2: Inclusion criteria regarding Group 4 (anaplastic thyroid cancer)

- Removal of the requirement of progression on prior therapy.
- Patients must not be at short term risk for life threatening complications (such as airway compromise or bleeding from locoregional or metastatic disease).
- Chemoradiation and/or surgery should be considered prior to study entry for those patients with locally advanced disease if those therapies are considered to be in the best interest of the patient.

Section 6.4.3: Prohibited concomitant therapy

- Addition that radiotherapy and surgery of lesions after progression based on RECIST may be allowed after documented discussion and approval by Novartis.

Section 6.6: Study drug preparation and dispensation

- To align with the EMA standard term list, the PDR001 pharmaceutical form has been updated to "Powder for solution for infusion". Change is made in Table 6-1.

Section 7.1.2.2: Patient demographics and other baseline characteristics

- Addition of BRAF V600 molecular status testing in tumor samples for patients in the anaplastic thyroid cancer group. Change is made in Table 7-8. Knowledge of the BRAF mutation status is not required for study entry.

[redacted]

Section 7.1.6: Follow up period

- Clarification on the description of the safety evaluations

Section 7.2.2.6 Cardiac assessment

- Change of ECG schedule from Screening, C1D1, C3D1, C6D1, and EoT to Screening and as clinically indicated. Change is made in Table 7-1 and Table 7-5

Section 7.2.3: Pharmacokinetic and immunogenicity assessments

[redacted]

Section 10: Statistical methods and data analysis

- Addition that several primary CSRs might be prepared which may include more than one indication.

Section 10.4.2: Statistical hypothesis, model, and method of analysis

- Removal of repeating information on primary analysis already detailed in section 10.

Section 10.5.3.1 and 10.5.3.2: Analysis set and grouping for the analyses

- Change of last day to On-treatment period definition from 150 days to 30 days after last dose of study medication (all patients will continue to be followed for 150 days after last dose)
- Change of Start date of post-treatment period from 151 days to 31 days after last dose of study medication
- Addition of safety summaries description

IRBs/IECs

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

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

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

Amendment 05 (30-Sep-2016)

Amendment rationale

The protocol is amended to increase the duration of contraception and safety follow-up periods post PDR001 treatment from 90 days to 150 days, using five times the upper limit of the half-life of 23 days and an added safety margin. These changes are related to an Urgent Safety Measure communicated on 08-Jun-2016 to all investigators. [redacted]

[redacted]

Therefore, after the start of a new antineoplastic therapy during the safety follow-up, only AEs and SAEs suspected to be related to PDR001 will be collected in order to focus on the collection of information relevant to PDR001; and concomitant medications will be recorded until the 30-day safety follow-up or the start of new antineoplastic, whatever occurred first.

[redacted]

Language relating to bone scans and other radiologic exams for evaluation of bone metastases is clarified.

Study status

The CPDR001X2101 study started enrollment on 27-Apr-2015. As of 27-Mar-2016, a total of 88 patients had been treated. 58 patients had been treated in the dose escalation part and 30 patients had been enrolled in Phase II part of the study (5 in NSCLC group, 12 in melanoma group and 13 in TNBC group). Enrollment to all cohorts in Phase II part is ongoing.

Changes to the protocol

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

[redacted]

Section 4.1: Study design

- For consistency across document reference to 3 and 4 weeks schedule has been added in description of study design
- Change of safety follow-up period from 90 days to 150 days. The extension of safety follow-up period to 150 days including safety assessments is reflected in Section 4.3, Section 6.3.2, Table 7-1, Section 7.1.6, Section 8.1.1, Section 8.2.2

Section 5.3: Exclusion criteria

- Change of period of use of contraception for female participant (exclusion criteria 24) and use of condom for sexually active males (exclusion criteria 25) from 90 days to 150 days after the last dose of PDR001. The extension of contraception to 150 days after last dose is reflected throughout the document. Change is made in Table 7-1 and Section 7.2.2.

[redacted]

Table 7-1: Visit evaluation schedule

- Addition of plasma collection for cytokines
- Addition that after initiation of new antineoplastic therapy, only AEs/SAEs suspected to be related to study treatment will be collected
- Addition that concomitant medications and non-drug procedures are reported until the 30-day safety follow-up or the start of new antineoplastic therapy, whatever occurred first. Change is made in Section 7.1.6

Section 7.1.6: Follow-up period

- Addition that PD and PK data collected during the follow-up period should be recorded on Biomarker blood sample CRF
- Addition of safety follow-up phone call or visit at 30, 90, and 150 days is reflected in Table 7-1, Section 7.1.6

Table 7-2: Disease assessment collection plan

- Clarification that bone scan is on whole body
- Addition that localized bone CT, MRI or x-ray are acceptable procedures for evaluating bone lesions

Section 7.2.3: Pharmacokinetics and immunogenicity assessments

- For consistency text and Table 7-6 were updated.

Table 7-6 Pharmacokinetic blood collection log and Table 7-7 Abbreviated pharmacokinetic blood collection log

- Addition of PK [redacted] sample collections at 150 days after last dose

[redacted]

Section 8.1: Adverse events

- Addition that after initiation of new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be reported. Change is made in Section 8.2

Section 10.4.2: Statistical hypothesis, model, and method of analysis

- Addition of indications to the group numbers

Section 10.5.3: Safety objectives

- Change of last day to On-treatment period definition from 90 days to 150 days after last dose of study medication
- Change of Start date of post-treatment period from 91 days to 151 days after last dose of study medication
- Section 10.5.4 PharmacokineticsLanguage has been changed to simplify analysis of IG data

[redacted]

[redacted]

Section 11.5: Publication of study protocol and results

- Language was updated to align with new clinical trial protocol template

Section 13 (References)

- New reference cited in Section 7.2.4 was added

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation with exception of contraception and safety follow-up period to 150 days related to an Urgent Safety Measure already implemented and that don't require IRB/EC approval.

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

Amendment 04 (13-May-2016)

Amendment rationale

In order to support the choice of the treatment dose and regimen for further development of PDR001, this amendment adds a group of patients with NSCLC treated with the alternative treatment regimen of 300 mg Q3W, in the phase II part. This regimen will be tested in addition to the RP2D of 400 mg Q4W. Inclusion of patients treated on a Q3W schedule will provide efficacy and safety information to support combination studies with agents that are given on a Q3W schedule such as common chemotherapy regimens.

In response to the rapidly changing approach to treatment of patients with melanoma and NSCLC, the eligibility criteria for patients with these diseases have been changed.

Patients with melanoma are no longer required to have received systemic therapy prior to being eligible for treatment with PDR001. All patients with BRAF V600 mutant melanoma must have received a BRAF inhibitor.

Patients with NSCLC may have received **no more than** one prior platinum-based doublet therapy.

For NSCLC, the patients with EGFR mutation-positive disease are now excluded as the published data suggest these patients receive limited benefit from treatment with single agent PD-1 inhibitors (Borghaei 2015). Patients with ALK translocation-positive NSCLC are eligible, as the currently available published dataset for these patients treated with PD-1 inhibitors is limited and therefore ALK translocation-positive patients will be included.

Language was updated to clarify when patients from the dose escalation part may switch to the RP2D.

[redacted]

This amendment adds a group of patients with anaplastic thyroid cancer in the phase II part. This is an exploratory group for a type of cancer without effective treatment options, but with evidence of clinical activity in one patient treated during the dose escalation phase of this study. The addition of these patients will allow an assessment of whether PDR001 may be active in this aggressive disease. For this group of patients only, focal irradiation is allowed to a target lesion if it is life-threatening, provided that other measurable disease remains. This exception is allowed to provide sufficient time for immunotherapy to act in patients with rapidly progressing disease. For patients with anaplastic thyroid cancer only, the archival diagnostic specimen or a new biopsy at study entry will be reviewed to confirm the diagnosis.

As different treatment regimens are used in this study, additional language was provided to clarify in which context it may or may not be allowed to switch from one regimen to another.

To further pursue the goal of allowing a preliminary assessment of efficacy relative to published data for similar patients being treated with other PD-1 checkpoint inhibitors, the exclusion criteria were updated to exclude patients with electrolyte abnormalities > CTCAE grade 2. The exclusion criteria were also updated to clarify that a washout period of 4 weeks is required only for live vaccines and to exclude patients who may not comply with the study for non-medical reasons. The ECOG performance inclusion criterion was also changed to ≤1.

In order to provide more flexibility in the treatment of symptoms caused by some tumor lesions and to allow patients to continue the study treatment, the prohibited concomitant therapy section was updated to allow localized radiotherapy for non-target lesions.

The inclusion criteria of the phase II part of the study require that the status is known for EGFR (and ALK if EGFR mutation-negative) for patients with NSCLC, and for BRAF V600 for patients with melanoma. Because the determination of EGFR, ALK, or BRAF V600 mutational status is not performed routinely as part of standard assessment of disease in all countries or study sites, this amendment includes the determination of these molecular parameters at molecular pre-screening by a local laboratory, or by a Novartis-designated laboratory if a local laboratory test is not feasible, for patients with a tumor of unknown status.

For the monitoring of the thyroid function, the measurement of free T4 is a more specific parameter as compared to total T4, therefore total T4 is removed and free T4 is added to the protocol assessments.

Current data suggest that the response to drugs targeting checkpoint inhibitors depend in part on the mutation burden in the tumor (Rizvi et al 2015). [redacted]

As Japan may join in the phase II part of the study, language specific for Japan has been added in the relevant sections of the protocol. This includes changes made to the exclusion criteria requested by a Health Authority.

The section on the reporting of SAEs has been updated to reflect a new procedure for the reporting of SAEs at Novartis.

Procedures for tumor evaluation were updated to include bone scans to be consistent with the methods of evaluation listed in the RECIST guideline (Section 14.1).

[redacted]

In various sections (e.g. Table 3-1, and Section 10), correction was made to clarify that the exposure data used in the Bayesian linear model will be the data collected in cycle 3, not the data collected after the first dose.

Minor inconsistencies/clarifications were also made throughout the document.

Study status

The CPDR001X2101 study started enrollment on 27 April 2015. As of 17 December 2015, a total of 58 patients had been treated in the study at the dose levels of 1, 3 and 10 mg/kg Q2W and 3 and 5 mg/kg Q4W. No patient has experienced any DLT and the toxicity profile appears to be similar to that of marketed inhibitors of PD-1. The PK data obtained from the dose escalation, and modeling of the exposure data, support the use of flat dosing for PDR001 of 400 mg given every 4 weeks as RP2D. The expected PDR001 Ctrough concentrations are in line with observed steady state mean Ctrough concentrations for pembrolizumab, which is approved with substantial efficacy in several cancer types. The data also support the use of 300 mg Q3W as an alternative dose regimen if it is more convenient for scheduling purposes, for example in combination treatment regimens.

Changes to the protocol

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

Section 1.2.1.2 Clinical experience:

- Update on the status of the currently ongoing CPDR001X2101 study.

Section 2.1 Study rationale and purpose:

- Addition of rationale for the inclusion of anaplastic thyroid cancer patients.

Section 2.2 Rationale for the study design:

- Addition of rationale for the inclusion of TNBC and anaplastic thyroid cancer patients in the phase II part of the study.

Section 2.3 Rationale for dose and regimen selection:

- Addition of rationale for the testing of alternative regimens.

Table 3-1 Objectives and related endpoints:

[redacted]

Section 4.1 Description of study design:

- Update of the Phase II part to include a group of patients with NSCLC treated with PDR001 given on a Q3W schedule and a group of patients with anaplastic thyroid cancer treated with PDR001 given on a Q4W schedule. Figure 4-1 was updated accordingly.
- Update of the treatment cycle duration to include a 21 day cycle if patients are treated on a Q3W schedule.

[redacted]

- Clarification that only one visit 90 days after the end of treatment is required for safety follow-up.

Section 5.1 Patient population:

- Language updated to reflect the addition of an anaplastic thyroid cancer group and one subgroup in the NSCLC group.

Section 5.2 Inclusion criteria:

- Inclusion criterion 2: addition of the language specific for Japan
- Inclusion criterion 4:
  - Clarification on prior therapies for all patients in part II
  - Additional patients with NSCLC have been added to test a 300 mg Q3W dose regimen in addition to the 400 mg Q4W regimen
  - A group of patients with anaplastic thyroid cancer has been added
  - The requirement for failure of systemic chemotherapy for patients with melanoma prior to being eligible for this study has been removed
  - Only patients with EGFR mutation-negative NSCLC can be included
  - Language has been changed to clarify that patients with NSCLC must have been treated with **no more than** one prior course of systemic chemotherapy (platinum-doublet)
- Inclusion criterion 5: modification to include patients with ECOG ≤ 1

Section 5.3 Exclusion criteria:

- Exclusion criterion 3: updated to exclude patients with electrolyte abnormality > CTCAE grade 2
- Exclusion criterion 6: added to exclude patients with history or current pneumonitis
- Exclusion criterion 10: addition of examples for indolent malignancy
- Exclusion criterion 12: updated to exclude patients with any condition that would prevent them from participating appropriately in the clinical study.
- Exclusion criterion 17: updated to require no live vaccine in the 4 weeks prior to first dose.
- Exclusion criterion 24: clarified the definition of women who are considered post-menopausal and not of child bearing potential

Section 6.1.1 Dosing regimen

- Clarification that if switching the dose of PDR001 to the RP2D results in an increase in the dose, then the patient must fulfill the criteria for intrapatient dose escalation as outlined in Section 6.2.3.4.

Section 6.2.3.4 Intra-Patient dose escalation:

- Clarification that intra-patient dose escalation includes also the use of a more frequent regimen
- Addition of a specification that during the phase II part of the study, intra-patient dose escalation or change of dosing regimen is not permitted.

[redacted]

Section 6.4.3 Prohibited concomitant therapy:

- Clarification that the use of localized palliative radiotherapy for the treatment of symptoms related to non-target lesions may be allowed after documented discussion with Novartis. Also, patients in the anaplastic thyroid cancer group may be allowed to receive limited-field radiotherapy to a target lesion that is life-threatening.

Table 7-1 Visit evaluation schedule:

- Update of the title to indicate that this visit evaluation schedule applies to all treatment regimens and that the duration of cycle will be adapted according to the treatment regimen.
- Addition of molecular pre-screening visit.
- Addition of the local or central assessment of EGFR, ALK, BRAF V600.
- Clarification that the results of the pregnancy tests performed during the safety follow-up need to be recorded in the source documentation only.
- Clarification of the wording on the tumor assessments to allow keeping the same frequency of tumor assessments independently from the duration of the cycle.
- [redacted]
- Clarification that only one visit 90 days after the end of treatment is required for safety follow-up.

Section 7.1.1 Molecular pre-screening:

- Addition of the molecular pre-screening to obtain the mutational status of EGFR (for NSCLC indication), ALK (for NSCLC indication if applicable) or BRAF V600 mutation (for melanoma indication).

Section 7.1.2.2 Patient demographics and other baseline characteristics:

- Addition of the possibility to test locally, or by a Novartis-designated laboratory if a local laboratory test is not feasible, for the status of EGFR and ALK mutations for NSCLC and BRAF V600 mutation status for melanoma, if the status is unknown at the time of enrollment of the patient.

Section 7.1.3 Treatment period:

- Clarification on the duration of the cycle according to the treatment regimen (i.e. 21 day or 28 day cycle).

Section 7.1.6 Follow-up Period

- Clarification that only one visit 90 days after the end of treatment is required for safety follow-up.

Table 7-2 Disease assessment collection plan

- Clarification of the wording on the tumor assessments to allow keeping the same frequency of tumor assessments independently from the duration of the cycle in Section 7.2.1 and in Table 7-2.
- Addition of a bone scan to evaluate patients with bone metastasis.

Table 7-4 Local clinical laboratory parameters collection plan:

[redacted]

- Replacement of Total T4 by Free T4.

Section 7.2.2.5.7 Pregnancy and assessment of fertility

- Clarification that the results of the pregnancy tests performed during the safety follow-up need to be recorded in the source documentation only.

Section 7.2.2.6.1 Electrocardiogram (ECG)

- Clarification that unique ECGs are collected only for Screening and EoT visits, as it does not apply to unscheduled assessments which can be either unique or multiple at a given visit depending on the needs to perform an unplanned ECG.

Table 7-6

- Update of the title to clarify the number of patients to whom this table applies, according to the group.
- Clarification of the timepoint for a Q3W schedule at Cycle 2Day 1 and Cycle 4Day 1 and addition of a 48h time window for this PK and IG sample collection

Table 7-7

- Clarification of the timepoint for a Q3W schedule at Cycle 2Day 1 and Cycle 4Day 1 and addition of a 48h time window for this PK and IG sample collection

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

- Update of the sample process description.

Section 7.2.4 Biomarkers

[redacted]

- Removal of the example of IFN-gamma, as this parameter might no longer be analyzed in this context.

Table 7-8

- Addition of samples to confirm diagnosis for anaplastic thyroid cancer patients.

Section 8 Safety monitoring and reporting

- The following sections were updated to reflect the new procedure for the reporting of SAEs at Novartis: 8.1.1; 8.2.2
- Section 8.2.2 was also updated to include language specific for Japan.

Section 10 Statistical methods and data analysis

- The following sections were updated to reflect the above described changes: 10; 10.4.1; 10.4.2; 10.5.2; 10.6.1; 10.6.2; 10.8: Table 10-3
- Section 10.4.4 was updated to include sensitivity analyses of ORR where the tumor response assessments are censored at the time of radiotherapy if a substantial number of patients are treated with palliative radiotherapy.

Section 13 References

- New references cited in the amendment 4 rationale and Section 2 were added.

[redacted]

IRB/IEC

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

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

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

Amendment 03

Amendment rationale

The primary purpose of this amendment is to provide greater clarity around the patient populations to be studied in the phase II part of the study, with the goal of allowing a preliminary assessment of efficacy relative to published data for similar patients being treated with other PD-1 checkpoint inhibitors. The inclusion and exclusion criteria have been modified accordingly. The modifications include restricting patients with NSCLC to no more than one prior platinum-based doublet chemotherapy regimen, with the exception of patients with ALK or EGFR-positive disease who must have been treated with a relevant tyrosine kinase inhibitor and a platinum-based doublet chemotherapy regimen. For patients with melanoma, all must have developed progressive disease after at least one systemic treatment regimen (for those with BRAF-wild type disease) or one systemic treatment regimen and a BRAF inhibitor (for those with BRAF-mutant disease). No disease-specific limitations are required for patients with triple negative breast cancer. As it was already the case in the previous version of the protocol, for all indications, patients who had previously received a PD-1 or PD-L1 checkpoint inhibitor are excluded from participating; those who had previously received other anticancer immunotherapies such as CTLA-4-directed therapy are eligible.

This amendment also allows the testing of a fixed/flat dose of PDR001 in the phase II part of the study. The use of a fixed/flat dose would reduce the risk of dosing errors and would also reduce drug product wastage. A decision about whether a fixed dose or a dose based on body weight is more appropriate will be made after assessing the PK data collected in the phase I part of the study, taking into consideration both PK and safety data. Patients enrolled in the dose escalation part may be given the option of switching to the RP2D (dose and schedule) after completing four cycles of treatment.

The requirement that patients have biopsiable disease and be willing to undergo biopsy during the phase II part of the study is adjusted to allow exceptions after documented discussion with Novartis. This amendment also introduces the possibility to stop the collection of biopsies, once a sufficient number of paired biopsies has been collected. This change may ease the burden of biopsies for patients.

The emergence of acquired resistance to therapy is a major problem for patients with cancer, and understanding the mechanism of acquired resistance to immunotherapies is an urgent goal of current research. Under this amendment, language has been added to allow the collection of

tumor tissue upon the development of acquired resistance to treatment. The purpose of this sample is to identify changes in the tumor that may underlie treatment resistance.

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

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

Japan is no longer planning to participate in this global study, therefore the language specific for Japan was removed from the protocol.

Minor inconsistencies/clarifications were made throughout the document.

Study status

The study started enrollment on 27 April 2015. As of 01 September 2015, a total of 44 patients have been treated in the study at the dose levels of 1, 3 and 10 mg/kg Q2W and 3 and 5 mg/kg Q4W. No patient has experienced any DLT in the completed cohorts. Seven patients have discontinued the study, four patients due to progression of disease and 3 patients due to SAEs which were not suspected to be related to study drug.

Changes to the protocol

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

Table 3-1 Objectives and related endpoints:

[redacted]

Section 4 Study design:

- Change in sample size in the phase II part of the study. Figure 4-1 was updated accordingly.
- Addition of language to introduce the possibility of treating patients at a flat dose in the phase II part of the study
- The safety follow-up was increased from 30 to 90 days. This change was applied throughout the protocol in Sections 4.3; 6.3.2; 7.1.6; 8.1.1; 8.2.2; 14.1.3.1.

Section 5.2 Inclusion criteria:

- Inclusion criterion 2: deletion of the language specific for Japan
- Inclusion criterion 4: addition of more detailed definition of the inclusion criteria for NSCLC and melanoma
- Inclusion criterion 6: adjusted to allow exceptions for patients in the phase II part of the study; and addition of the possibility to stop the collection of biopsies, once a sufficient number of paired biopsies has been collected.

Section 5.3 Exclusion criteria:

- Clarification of exclusion criterion 5

[redacted]

- Addition of ocular melanoma as exclusion criterion 10
- Addition of a washout period for immunotherapies including CTLA-4 antagonists in criterion 12
- Addition of total hysterectomy in the definition of female sterilization and update of the definition of highly effective contraception in exclusion criterion 23
- Addition of exclusion criterion 24, which excludes sexually active male subjects who do not use a condom during intercourse

Section 6.1 Study treatment:

- Addition of the possibility to switch to treatment with PDR001 at the RP2D (dose and schedule) for patients enrolled in the phase I part of the study.

Section 6.2.3.1 Bayesian dose exposure model:

- Clarification that the exposure data used in the model will be the data collected in cycle 3, not the data collected after the first dose.

Section 6.6 Study drug preparation and dispensation:

- Clarification that also dose interruptions must be recorded in the dosage administration record CRF.

Section 7.1 Visit flow and visit schedule:

- Clarification of the visit window for the pregnancy test at screening

Table 7-1 Visit evaluation schedule:

- Addition of the safety follow-up at 60 days and 90 days after the last dose of study treatment, as well as related assessments.
- Addition of the new tumor biopsy sample collection at time of disease progression

Section 7.1.2.2 Patient demographics and other baseline characteristics:

- Addition of the collection of information regarding the status of EGFR and ALK mutations for NSCLC and BRAF V600 mutation status for melanoma in the phase II part of the study.

Section 7.1.3 Treatment period:

- Deletion of redundant text

Section 7.1.4 Discontinuation of study treatment:

- Deletion of text that does not apply in this protocol

Section 7.1.6 Follow-up period:

- Addition of the 60 day and 90 day safety follow-up and associated assessments
- Clarification that also in case of clinical progression, the patient would not be followed for disease progression.
- Addition of the reference to the end of post treatment phase disposition CRF.

Table 7-2 Disease assessment collection plan

- Addition of wording relating to the disease progression follow-up to align with the text in Section 7.2.1.

[redacted]

- Correction of the Table 7-2 regarding the requirement for brain CT/MRI to align with standard clinical practice.

Section 7.2.2.3 Height and weight:

- Clarification of the units for these parameters

Section 7.2.2.5.6 Cytokines

- Clarification that the sample analysis will be performed locally

Section 7.2.2.5.7 Pregnancy and assessment of fertility

- Addition of pregnancy tests during the safety follow-up period

Table 7-6

- Removal of the dose reference ID which is not required for the study sites to understand the PK and IG sample collection schedule
- Clarification of the time point 672 hours post-dose for the Q4W schedule

Section 7.2.4 Biomarkers

- Addition of the assessment of mechanisms of resistance to PDR001

Section 10 Statistical methods and data analysis

- The following sections were updated to reflect the above described changes: 10.4.2; 10.5.3.1; 10.6.2; 10.7; 10.8

Section 13 References

- New references cited in the Section 10.8 were added.

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

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

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

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

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

Amendment 02

Amendment rationale

The landscape of treatment with immunomodulatory therapy in oncology is evolving rapidly, and particularly so with antibodies that target the PD-1/PD-L1 interaction. In response to emerging publically available clinical data this amendment changes the disease indications that

[redacted]

will be studied. Specifically, the phase II dose expansion part of the study will now focus on patients with NSCLC, melanoma and triple negative breast cancer; the planned expansion groups for patients with gastric and esophageal cancer, colorectal cancer and anal cancer have been removed. The inclusion criteria affected by these changes have been amended accordingly. The total number of patients treated in each group of patients in the Phase II part will remain unchanged.

Removal of the gastric/esophageal, colorectal and anal cancer groups also affects the role of the PD-L1 biomarker, which was an inclusion criterion for these patients. Published data for PD-L1 expression and tumor response in multiple diseases suggests a positive correlation between PD-L1 expression in tumor and response to treatment. Nevertheless, tumor responses have been reported in patients with low PD-L1 expression. In addition, the most appropriate assay and criteria for defining "positive" tumors are uncertain and an area of active clinical investigation. Therefore, no molecular screening for PD-L1 will be performed to select patients however PD-L1 expression will be assessed retrospectively for all patients.

At the time of RP2D/MTD determination, the amount of efficacy data collected may be limited. To provide greater confidence in choosing the most appropriate dose for further development, the study design has been updated to allow testing of two doses of PDR001 in one disease indication during the phase II part.

Furthermore a few exclusion criteria were clarified:

- Patients with active autoimmune disease are excluded.
- In order to ensure that all patients with HIV, active HBV or active HCV infection are excluded, the wording in the exclusion criteria was adjusted and the corresponding tests were added at Screening.

In addition, collection of a sample for cytokine assessment (IL-6 and IFN-γ) was added for all patients at Screening. This baseline sample will serve as a comparator for those patients who need the follow-up assessment of cytokines (i.e. if the patient has an adverse event suspected to be a cytokine release syndrome).

In Section 6.4.3 Prohibited concomitant therapy, the wording related to the use of systemic steroid therapy during the course of study was adjusted in order to provide more flexibility for patients who would need such therapy for treatment of acute conditions.

In order to align the collection and analysis of pharmacodynamic biomarkers with preclinical evidence on the timing of immune response in tumor after therapy with PD-1 blocking antibodies, the collection of the on-treatment new tumor biopsy sample was moved from C2D1 (i.e. between C2D1 and C2D15) to C3D1 (i.e. between C3D1 and C3D15).

Minor inconsistencies/clarifications were made throughout the document.

Study status

The study started enrollment on 27 April 2015. As of 28 May 2015, 6 patients have been enrolled in the first cohort at the dose of 1 mg/kg.

[redacted]

Changes to the protocol

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

Section 2.1 Study rationale and purpose:

- Change of the indications in the phase II part.
- The groups were changed throughout the protocol including Figure 4-1.

Section 4.1 Description of study design:

- Removal of the molecular screening for PD-L1 expression. Reference to molecular screening was removed throughout the protocol.
- Addition of the possibility to test a second dose level in one or more indications during the Phase II part.

Section 5.2 Inclusion criteria:

- Inclusion criterion 4 was updated to reflect the change in the tumor types to be included in the phase II part.

Section 5.3 Exclusion criteria:

- Change in exclusion criterion 5 to clarify that patients with active autoimmune disease are excluded.
- Change in exclusion criterion 7 to clarify that any patient with HIV infection is excluded.
- Clarification of exclusion criterion 13 excluding patient that require chronic treatment with systemic steroids.
- Clarification of exclusion criterion 14
- Further specification of exclusion criterion 17 in relation to prior radiotherapy for patients enrolled in the Phase II part.

Section 6.4.3 Prohibited concomitant therapy

- Update of the wording on the use of systemic steroid therapy during the course of the study.

Section 6.5.1 Patient numbering

- Addition of wording to ensure patient number will be unique and unchanged for a patient.

Section 7.2.2.5 Laboratory evaluations

- Addition of HIV, HBV and HCV assessments at Screening.
- Addition of the collection of a sample for cytokine assessment at Screening.
- Changes were made to Table 7-1 and Table 7-4 accordingly.

Section 7.2.2.6.1 Electrocardiogram (ECG)

- Wording clarification on the number of ECGs to be performed at Screening, EoT and Unscheduled visits was provided.

Section 7.2.4 Biomarkers

- Change of timepoint for new tumor biopsy sample collection from between C2D1 and C2D15 to between C3D1 and C3D15.

[redacted]

Section 8.2.2 Reporting

- removal of wording related to the molecular screening.
- removal of the language specific for Japan, as SAEs will be reported in English for this study in Japan.

Section 10 Statistical methods and analysis

- Sections 10, 10.1.3, 10.4.2, 10.5.2, 10.6.1, 10.6.2, 10.7 and 10.8 were updated to align with the changes described above for the other sections of the protocol.

[redacted]

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

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

Amendment 01

Amendment rationale

This amendment addresses the following revision requested by a regulatory authority:

- To reduce the starting dose of PDR001 to 1 mg/kg administered once every two weeks, as requested by a regulatory authority.

Additional minor corrections/clarifications were also made. The details are provided in the below section Changes to the protocol.

Changes to the protocol

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

Section 6.2.1 Starting dose rationale:

- Change of starting dose to 1 mg/kg.
- The starting dose was updated throughout the protocol.

Minor corrections/clarifications in Section 6.3.1 and Table 7-2.

IRB/IEC/HA Approval

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

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

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

It has long been postulated that the immune system is able to recognize and kill tumor cells, and that immune-surveillance may be an ongoing process in healthy people that is important for eliminating malignant cells before a cancer can develop. This theory is borne out by the markedly increased risk of a variety of solid and hematological malignancies in immunosuppressed patients following solid organ transplantation (Vesely et al 2011). The ability of the immune system to attack and kill an established cancer to a clinically meaningful degree was first demonstrated by the success of donor lymphocyte infusion for treating relapsed chronic myeloid leukemia following allogeneic bone marrow transplant (Kolb et al 1990). The activity of interleukin 2 (IL2) and interferon alpha (IFN-α) in patients with renal cell carcinoma and melanoma demonstrated that immunotherapy can be active in solid tumor oncology, albeit in a minority of patients (Kirkwood 1985, Creagan 1990, Fyfe 1996).

The activity of cytotoxic T-lymphocytes is the result of both stimulatory and inhibitory signals. Besides the activation resulting from the interaction of the antigen presented in the major histocompatibility complex (MHC) on the antigen-presenting cell (APC) with the T-cell receptor (TCR), there are inhibitory signals mediated by checkpoint molecules, such as CTLA-4 or PD-1, which protect healthy tissues from excessive T-lymphocyte activation (Blank 2014). PD-1 is a critical checkpoint receptor that is expressed by T cells upon activation (Freeman 2008). It is also expressed by B cells, NK cells, dendritic cells, and activated monocytes. The ligands for PD-1: Programmed Death-Ligand 1 (PD-L1) and Programmed Death-Ligand 2 (PD-L2) are expressed by macrophages, monocytes and dendritic cells, and can be induced on numerous cell types (T cells, endothelial cells, and tumor cells) during inflammation (Keir et al 2008). Engagement of PD-1 by its ligands PD-L1 and PD-L2 transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function (Riley 2009). The PD-1 checkpoint pathway is thought to act primarily in peripheral tissues to dampen ongoing immune responses and/or to prevent autoimmunity.

During tumorigenesis, cancer cells from a wide range of tumor types exploit immune checkpoint pathways, such as PD-1, to avoid detection by the adaptive immune system (Murphy 2011). Blockade of the PD-1 pathway has been shown to lead to increased numbers of effector T cells through induction or expansion and improved cytolytic activity towards tumors. Additionally, PD-1 blockade is associated with accumulation of effector T cells and reduced numbers of regulatory T cells (Tregs) at the tumor site. (Wang 2009, Mangsbo 2010, Mkrtichyan 2011, Rosenblatt 2011).

Monoclonal antibody (mAb) inhibitors of immunological checkpoints, including PD-1 and PD-L1, have demonstrated significant antitumor activity in patients with various solid tumors with less toxicity than broad immune activators, such as IL2 and IFN-α. PD-1 is a particularly important immunological target, with inhibitors active across a variety of solid tumors. Two mAbs targeting PD-1, pembrolizumab and nivolumab, have demonstrated significant single agent activity in melanoma, non-small cell lung carcinoma (NSCLC), triple negative breast cancer (TNBC) and other solid tumors (Topalian 2012, Hamid 2013b, Topalian 2014, Seiwert 2014, Powles 2014, Garon 2015, Moreno and Ribas 2015, Robert 2015). In patients with

[redacted]

previously treated, unresectable melanoma the response rates to pembrolizumab and nivolumab were 34% and 31%, respectively; and the PFS were 50 weeks and 9.7 months, respectively (Ribas 2014, Topalian 2014). In patients with advanced, previously untreated non-small cell lung cancer the response rates to pembrolizumab and nivolumab were 26% and 30%, (Rizvi 2014, Gettinger 2014).

1.2 Introduction to the investigational treatment

1.2.1 Overview of PDR001

PDR001 is a high-affinity, ligand-blocking, humanized anti-PD-1 IgG4 antibody that blocks the binding of PD-L1 and PD-L2 to PD-1. PDR001 recognizes PD-1 in cynomolgus monkeys and shows functional activity in vitro/ex vivo. For further details, please refer to the [PDR001 Investigator's Brochure].

1.2.1.1 Non-clinical experience

PDR001 binds specifically and with high affinity to human PD-1. In Biacore assays, the KD of PDR001 on human PD-1 is 0.827 nM. In ex vivo lymphocyte stimulation assays using human blood, PDR001 enhances interleukin-2 (IL-2) production by approximately 2 fold in response to super antigen stimulation with Staphylococcal enterotoxin B (SEB). PDR001 does not cross-react with rodent PD-1, and cannot be evaluated in murine tumor models. It does cross-react with cynomolgus monkey PD-1, and is functionally active, making cynomolgus monkey a relevant species for toxicology studies. The affinity of PDR001 for cynomolgus PD-1 is 0.929 nM, nearly the same for human PD-1, as noted above.

A GLP tissue cross reactivity study using frozen human and cynomolgus monkey tissues was also done in support of the safety of PDR001. There was no unexpected binding observed. The non-clinical toxicology of PDR001 was evaluated in a five week GLP toxicology study in cynomolgus monkeys with safety pharmacology endpoints and an eight week recovery. All main phase data as well as recovery pathology data are reported here. All other recovery phase data are pending. Repeat administration of PDR001 to monkeys was well tolerated at all doses tested in the GLP toxicology study. No test article-related in-life, mortality, organ weight changes, or macroscopic findings were noted. There were no PDR001-related effects seen in any of the safety pharmacology endpoints assessed (cardiovascular, neurobehavioral, and respiratory). Macrophage infiltrates into the splenic white pulp were observed in animals given 100 mg/kg/week and mononuclear cell infiltrates, often associated with fibrosis, around the injection site blood vessel (saphenous vein) in a few animals given ≥25 mg/kg/week. These PDR001-related microscopic changes were fully reversible after an eight week recovery.

The following changes were noted in main phase and recovery treated animals as well as control recovery animals. Mostly low grade changes were noted in several tissues in the form of mononuclear infiltrates in the vascular and perivascular space. In general, in most organs, vascular/perivascular changes were limited to one or a few blood vessels in each organ and sometimes involved a segment of a blood vessel with occasional vessel wall degeneration. No evidence of parenchymal damage was associated with the vascular/perivascular changes in any of the organs examined and the changes were not associated with any frank tissue injury. While these effects were not exclusive to treated animals, because of their nature and close association

with the expected pharmacology of PD1 blockade, a potential PDR001 related effect cannot be excluded. There were no test article related effects seen in the cardiovascular assessments. All other microscopic findings were considered spontaneous or otherwise unrelated to PDR001 administration.

Dose-dependent exposure to PDR001 in each dose group was confirmed. A pharmacodynamic *ex vivo* superantigen stimulated whole blood assay measuring IL-2 release was performed. Blood from untreated control animals showed augmentation of IL-2 release when PDR001 was added *ex vivo*, whereas blood from treated animals at all doses did not show augmented IL-2 release, indicating target engagement and inability to further dis-inhibit the SEB induced response with the further addition of PDR001. The Highest Non-Severely Toxic Dose (HNSTD) dose in this study was 100 mg/kg. PDR001 has a favorable safety profile in monkeys that supports a projected human starting dose of 1 mg/kg in the first in human study CPDR001X2101. For further details, please refer to the [PDR001 Investigator's Brochure].

1.2.1.2 Clinical experience

This study started enrollment on 27 April 2015. As of 17 December 2015, a total of 58 patients had been treated in the study at the dose levels of 1, 3 and 10 mg/kg Q2W and 3 and 5 mg/kg Q4W. No patient has experienced any DLT and the toxicity profile appears to be similar to that of marketed inhibitors of PD-1 (pembrolizumab US label, nivolumab US label). The PK data obtained from the dose escalation, and modeling of the exposure data, support the use of flat dosing for PDR001 of 400 mg given every 4 weeks as RP2D. The expected PDR001 Ctrough concentrations are in line with observed steady state mean Ctrough concentrations for pembrolizumab, which is approved with substantial efficacy in several cancer types (pembrolizumab US label). The data also support the use of 300 mg Q3W as an alternative dose regimen if it is more convenient for scheduling purposes, for example in combination treatment regimens.

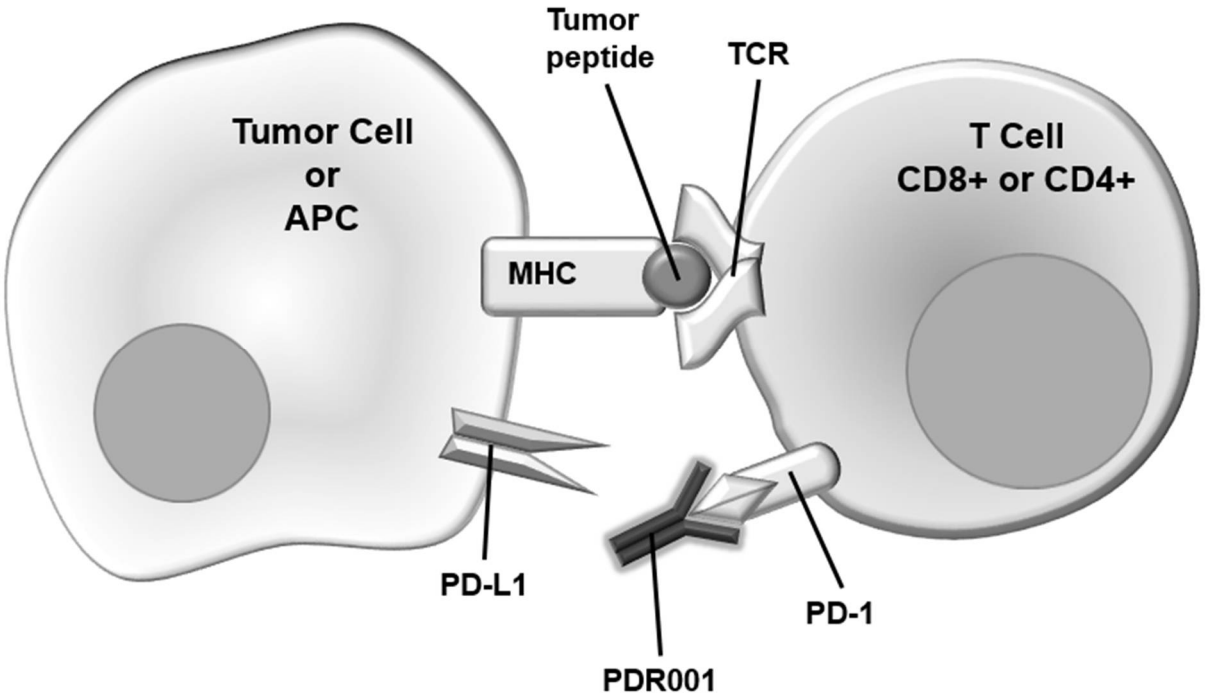
2 Rationale

2.1 Study rationale and purpose

This FIH, phase I/II clinical study of PDR001 will characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of PDR001 administered i.v. as a single agent. By blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2, PDR001 inhibits the PD-1 immune checkpoint, resulting in activation of an antitumor immune response by activating effector T-cells and inhibiting regulatory T-cells (Hamid and Carvejal 2013a). From ongoing studies with anti-PD-1 antibodies, such as nivolumab and pembrolizumab, it is evident that PD-1 checkpoint inhibition results in clinically important anti-tumor activity (Topalian 2012, Hamid 2013b, Topalian 2014, Seiwert 2014).

[redacted]

Figure 2-1 Blockade of PD-1/PD-L1 interaction by PDR001



APC: Antigen Presenting Cell; MHC: Major Histocompatibility; TCR: T Cell Receptor

This study is designed both to establish a recommended dose and schedule for the anti PD-1 antibody, PDR001, and to make a preliminary assessment of PDR001 antitumor activity in NSCLC, melanoma, anaplastic thyroid cancer and TNBC. This FIH study is designed to establish if PDR001 is tolerable and active, and provide data to support future disease-specific development.

2.2 Rationale for the study design

This is an open-label, non-randomized phase I/II study of single-agent PDR001. The phase I part of the study is a PK- and dose limiting toxicity (DLT)-guided dose escalation. Cohorts of patients will receive escalating doses of PDR001 until a dose is reached, which fulfills one of the following criteria:

- Achieves PDR001 exposure (Area Under the Curve: AUC) comparable to the AUC reported for pembrolizumab and nivolumab at the doses being used in the ongoing phase III studies
- Is the maximum tolerated dose (MTD), based on occurrence of dose limiting toxicities (DLTs).

During their early development, both nivolumab and pembrolizumab were escalated to high doses (10 mg/kg every 2 weeks) without reaching a MTD. Both antibodies have demonstrated similar response rates across a wide range of doses and are now being developed at doses of 2-3 mg/kg every 2-3 weeks (Topalian 2014, Robert 2014). PDR001 binds to PD-1 with high affinity and inhibits the pharmacodynamic activity of PD-1 binding. With the reasonable assumption that PDR001 will have similar PK and pharmacodynamic properties as pembrolizumab and nivolumab the PK-guided dose escalation approach being taken in this

[redacted]

study is expected to identify an active dose of PDR001 without the need to escalate to very high doses or to evaluate a large number of dose levels. In addition, pharmacodynamic parameters such as CD8+ tumor infiltrating lymphocytes (TILs) and expression of selected immune response markers will be used to further support the choice of an active dose of PDR001.

The phase II part of the study will begin after the recommended phase 2 dose (RP2D) is determined. The primary objective of the phase II part is to evaluate PDR001 antitumor activity, in two "benchmark diseases", NSCLC and melanoma, where response rates to nivolumab and pembrolizumab are known, as well as in TNBC in which antitumor activity was reported for pembrolizumab (Nanda 2014, Moreno and Ribas 2015). In response to evidence of clinical activity in a patient during the dose escalation phase of this study, a small group of patients with anaplastic thyroid carcinoma will also be enrolled to preliminarily assess any clinical activity in this very aggressive disease that lacks effective treatment options. Preliminary data from the early clinical studies of nivolumab and pembrolizumab, as well as the anti-PD-L1 antibodies, MPDL3280A and MEDI4736 indicate that PD-L1 protein expression both on tumor cells and on tumor-infiltrating immune cells correlates with clinical response to these agents (Topalian 2012, Weber 2013, Taube 2014, Powles 2014, Creelan 2014). PD-L1 expression will be measured for all patients enrolled, however, patients will not be selected for PD-L1 expression, since the response rates to nivolumab and pembrolizumab available in the literature are based on unselected populations. In these published studies, patients without PD-L1 expression also responded to treatment with anti-PD-1 immunotherapy (Topalian 2012, Hamid 2013b, Robert 2014, Motzer 2015).

2.3 Rationale for dose and regimen selection

The starting dose and regimen of 1 mg/kg PDR001 administered once every 2 weeks was selected for this study and is based on the preclinical safety, tolerability, and PK data observed in the cynomolgus monkey, incorporating the standard safety margin applied in advanced oncology indications, as described in Section 6.2.1. The dose of PDR001 will be escalated in sequential cohorts using a PK-guided approach to achieve an AUC comparable to the active range observed with nivolumab and pembrolizumab, as described in Section 2.2 and Section 10.4.2. PDR001 will be administered i.v. every 2 weeks based on an expected half-life of 10-20 days, and consistent with a schedule commonly used for humanized monoclonal antibodies. In order to identify recommended treatment regimens for future use, alternative regimens (e.g. Q3W, Q4W) will also be tested.

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
Phase I part: To estimate the RP2D and/or the MTD for PDR001	Phase I part: ● The exposure ($AUC_{(0\text{-}336h)}$) after first dose of treatment at cycle 3 ● The incidence of DLTs	
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).	
Secondary		Refer to Section 10.5.1.
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	
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	
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	
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), per RECIST 1.1 and irRC	
Phase II part: To evaluate the preliminary anti-tumor activity of PDR001	ORR per immune related Response Criteria (irRC) and PFS, DOR, DCR per RECIST 1.1 and irRC	

[redacted]

[redacted]

[redacted]

[redacted]

4 Study design

4.1 Description of 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 will be administered i.v. every 2 weeks (or every 3 or 4 weeks) until a patient experiences unacceptable toxicity, progressive disease as per irRC and/or treatment is discontinued at the discretion of the investigator or the patient. Patients should not discontinue treatment based solely on progressive disease per RECIST. The study design is summarized in Figure 4-1.

Phase I dose escalation part

During the phase I part of the study, cohorts of patients will be treated with PDR001 until the MTD is reached or a lower RP2D is established. It is expected that an RP2D will be established before the MTD is reached, as it was observed with other anti-PD-1 antibodies. 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 will also be 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 Section 6.2.3). Data from several PD-1 and PD-L1 inhibitors already in clinical trials have demonstrated that inhibiting the PD-1/PD-L1 interaction can result in tumor response across a broad range of solid tumors (Topalian 2012, Hamid 2013b, Seiwert 2014, Segal 2014, Powles 2014, Herbst 2014); therefore, the Phase I part of the study will include patients with solid tumors, and is not limited to specific types of tumors.

Potential change to an alternative dosing schedule during the escalation part

If emerging data indicate that a less frequent dosing regimen such as once every 4 weeks is more appropriate, then a new cohort of patients will be enrolled and treated with this schedule, and subsequent escalation may proceed using the new regimen. A modification of the dosing regimen would be based on emerging PK, PD, and safety assessments.

Phase II part

Once the MTD and/or RP2D have been 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 4-1. Please refer to Section 5.1 for further details.

Groups 1a, 1b and 2 will enroll approximately 60 patients each, group 3 will enroll approximately 40 patients, and group 4 will enroll 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

[redacted]

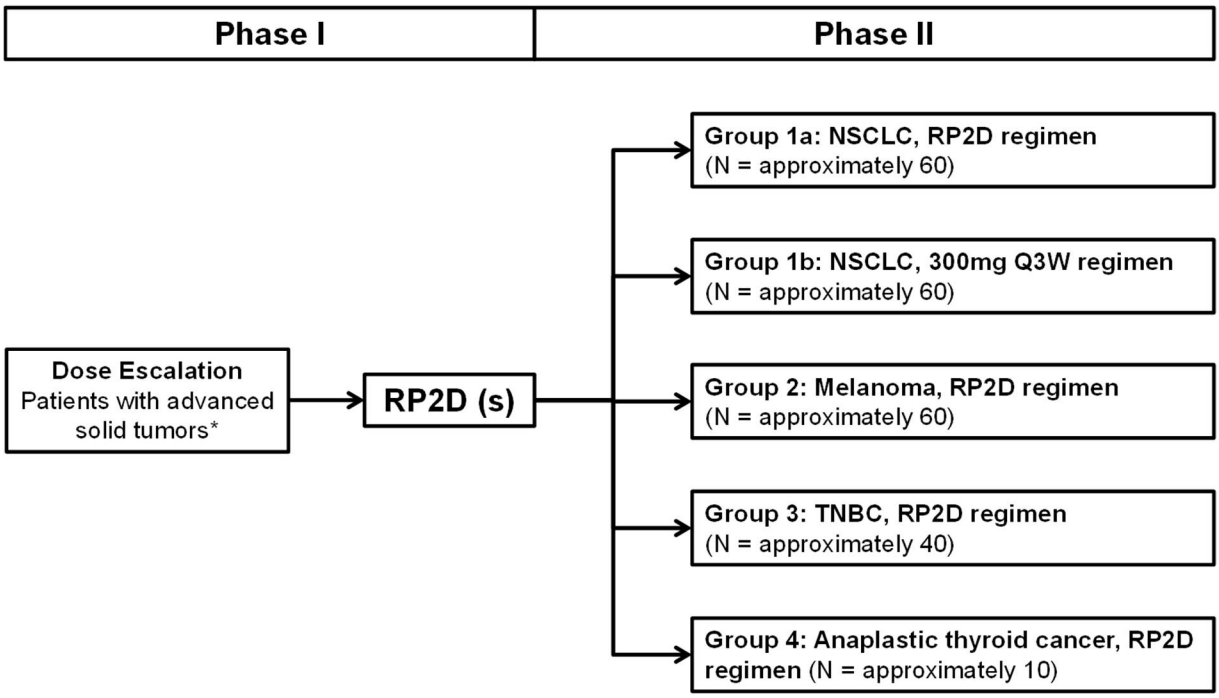
approximately 40 patients based on feasibility of enrollment and if PDR001 appears to be active (at least one response or other efficacy data show preliminary anti-tumor activity in the first 10 patients) in this disease. A Bayesian design will be used in order to estimate ORR within each group. Details of the sample size calculations leading to the patient numbers are provided in 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 4-1 Study design



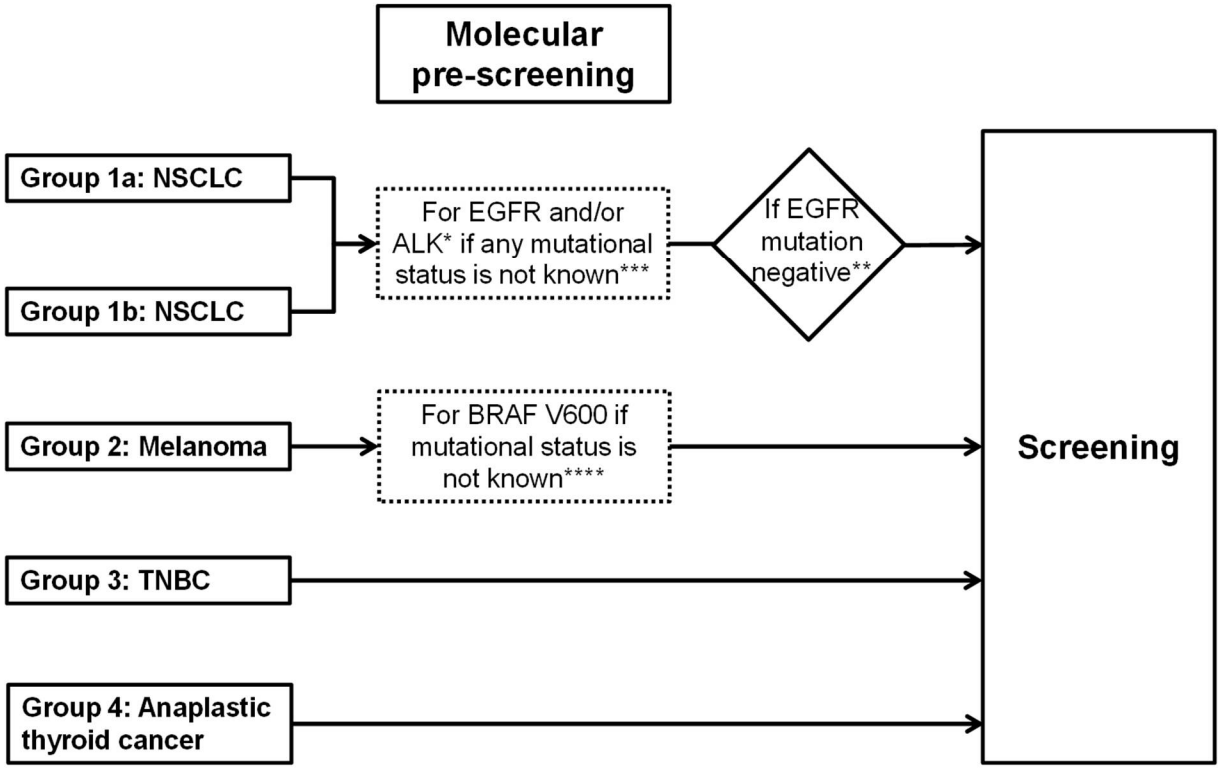
* In the dose escalation, at least 21 patients are required to define the MTD; however, fewer than 21 patients may be treated if the RP2D is achieved prior to determination of the MTD. One of the RP2Ds may be the MTD.
After a preliminary assessment of the safety profile in the phase I part, a decision may be made to test up to two regimens of PDR001 during the phase II part.

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

Molecular pre-screening

To enter the screening phase of this study, patients must provide written documentation of EGFR (for NSCLC indication), ALK (for NSCLC indication if negative for EGFR mutation) or BRAF V600 mutation (for melanoma indication) (see Section 7.1.1 for details) and complete the molecular pre-screening assessment if needed.

Figure 4-2 Molecular pre-screening



* ALK and EGFR can be tested simultaneously
** Defined as negative for exon 19 deletions and for the L858R mutation in EGFR at a minimum; however, if more extensive EGFR mutation testing has been performed, the tumor must not harbor any known activating EGFR mutations in Exons 18-21 in order to be considered EGFR mutation-negative
*** Patients with ALK translocation-positive NSCLC must have had disease progression following treatment with a corresponding inhibitor. Patients with ALK translocation-negative NSCLC must have had disease recurrence or progression during or after no more than one prior systemic chemotherapy regimen (platinum doublet-based)
**** Patients with V600 mutation positive melanoma must have clinical or radiological evidence of disease progression during or after treatment with a BRAF inhibitor alone or in combination with other agents. Patients without BRAF mutation are not required to have received a prior therapy

Screening period

The screening period begins once the patient has signed the study informed consent. Patients will be evaluated against study inclusion and exclusion criteria (Table 7-1 and Section 5.2, Section 5.3 and Section 7.1.2).

An archival or newly obtained tumor biopsy sample will be required to be submitted to a Novartis designated central laboratory for biomarker assessment at baseline. Please refer to Section 7.2.4 for further details.

Treatment period

The treatment period will begin on Cycle 1 Day 1. For the purpose of scheduling and evaluations, for Q2W and Q4W regimens, a treatment cycle will consist of 28 days; for a Q3W regimen, a treatment cycle will consist of 21days. Further details are provided in Table 7-1 and Section 7.1.3.

150-day follow-up (FU) period

For 150 days after the last administration of study treatment, patients will be followed up for safety evaluations (Table 7-1 and Section 7.1.6).

Disease progression FU

Patients who discontinue study treatment for any reason other than disease progression, lost to follow-up or death will be followed up for progression of disease (Section 7.1.6). The disease progression follow-up will be performed until at least 80% of all patients enrolled in each disease group of the phase II part of the study have had progression of disease or discontinued the study for any reason.

Survival FU

Patients will be followed for survival (Section 7.1.6) until the end of the study is reached.

4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned. However, in the phase I part, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. (Section 10.7)

4.3 Definition of end of the study

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

- the study is terminated early,

or

[redacted]

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

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

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

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible for End of Treatment (EOT) visit and the assessments for EOT should be performed as described in Section 7.1.4 for a discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or independent ethics committees (IECs) of the early termination of the trial.

5 Population

5.1 Patient population

The phase I part of the study will be conducted in adult patients with advanced solid tumors.

The phase II part of the study will be conducted in adult patients with four distinct diseases (melanoma, NSCLC, TNBC and anaplastic thyroid cancer) as outlined in Figure 4-1 and Section 5.2.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

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

1. Written informed consent must be obtained prior to any procedures
2. Age ≥ 18 years. **[For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.]**
3. Phase I part: Patients with advanced/metastatic solid tumors, with measurable or non-measurable disease as determined by RECIST version 1.1 (refer to Appendix 1), who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists.
4. Phase II part: Patients with advanced/metastatic solid tumors, with at least one measurable lesion as determined by RECIST version 1.1, who have progressed following their last prior therapy, and fit into one of the following groups:
   - Groups 1a and 1b: NSCLC:

[redacted]

Patients with NSCLC must have had disease recurrence or progression during or after no more than one prior systemic chemotherapy regimen (platinum doublet-based) for advanced or metastatic disease. Prior maintenance therapy is allowed (e.g. pemetrexed, erlotinib, bevacizumab).

Only patients with EGFR mutation-negative tumor are eligible (defined as negative for exon 19 deletions and for the L858R mutation in EGFR at a minimum; however, if more extensive EGFR mutation testing has been performed, the tumor must not harbor any known activating EGFR mutations in Exons 18-21 in order to be considered EGFR mutation-negative). All patients must be tested for EGFR mutational status and, for ALK translocation status if no mutation is detected in EGFR. Patients with ALK translocation-positive NSCLC must have had disease progression following treatment with a corresponding inhibitor and no more than one systemic chemotherapy regimen (platinum doublet-based), in any sequence.

- Group 2: Melanoma:

All patients must have been tested for BRAF mutations. Patients with V600 mutation positive melanoma must have clinical or radiological evidence of disease progression during or after treatment with a BRAF inhibitor alone or in combination with other agents.

Patients without BRAF mutation are not required to have received a prior therapy.

- Group 3: Triple negative breast cancer
- Group 4: Anaplastic thyroid cancer
  - Patients are not required to have received or progressed on a prior therapy.
  - Patients must not be at short term risk for life threatening complications (such as airway compromise or bleeding from locoregional or metastatic disease,).
  - Chemoradiation and/or surgery should be considered prior to study entry for those patients with locally advanced disease if those therapies are considered to be in the best interest of the patient.

5. ECOG Performance Status ≤ 1.
6. Patient must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution's guidelines. Patient must be willing to undergo a new tumor biopsy at baseline or at molecular pre-screening if applicable, and during therapy on this study. For patients in the phase II part of the study, exceptions may be granted after documented discussion with Novartis. After a sufficient number of paired biopsies are collected, the decision may be taken to stop the collection of biopsies.

5.3 Exclusion criteria

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

1. Presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within the prior 2 weeks.
2. History of severe hypersensitivity reactions to other mAbs
3. Patient having out of range laboratory values defined as:

[redacted]

- Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 40 mL/min
- Total bilirubin > 1.5 x ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
- Alanine aminotransferase (ALT) > 3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if ALT > 5 x ULN
- Aspartate aminotransferase (AST) > 3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if AST > 5 x ULN
- Absolute neutrophil count < 1.0 x 10^9/L
- Platelet count < 75 x 10^9/L
- Hemoglobin (Hgb) < 8 g/dL
- Potassium, magnesium, calcium or phosphate abnormality > Common Terminology Criteria for Adverse Events (CTCAE) grade 2

4. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
   - Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia
   - QTcF >470 msec on screening ECG or congenital long QT syndrome
   - Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry
5. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
6. History of drug-induced pneumonitis or current pneumonitis.
7. Active infection requiring systemic antibiotic therapy.
8. Human Immunodeficiency Virus (HIV) infection.
9. Active HBV or HCV infection.
10. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy (e.g. ductal carcinoma in situ, some low grade lymphomas, high-grade prostatic intraepithelial neoplasia, monoclonal gammopathy of undetermined significance); and completely resected carcinoma in situ of any type.
11. Patients with ocular melanoma
12. Any condition that would prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results.
13. Systemic anti-cancer therapy within 2 weeks of the first dose of study treatment. For cytotoxic agents that have major delayed toxicity, e.g. mitomycin C and nitrosoureas, 4

[redacted]

weeks is indicated as washout period. For patients receiving anticancer immunotherapies such as CTLA-4 antagonists, 6 weeks is indicated as the washout period.

14. Prior PD-1- or PD-L1-directed therapy.
15. Patients requiring chronic treatment with systemic steroid therapy, other than replacement-dose steroids in the setting of adrenal insufficiency. Topical, inhaled, nasal and ophthalmic steroids are not prohibited.
16. Patients receiving systemic treatment with any immunosuppressive medication (other than steroids as described above).
17. Use of any live vaccines within 4 weeks of initiation of study treatment.
18. Major surgery within 2 weeks of the first dose of study treatment (mediastinoscopy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery).
19. Radiotherapy within 2 weeks of the first dose of study drug, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass. To allow evaluation for response to treatment, patients enrolled in the phase II part must have remaining measurable disease that has not been irradiated.
20. Participation in an interventional, investigational study within 2 weeks of the first dose of study treatment.
21. Presence of ≥ CTCAE grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if ≥ CTCAE grade 3) due to prior cancer therapy.
22. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GMCSF, M-CSF) ≤2 weeks prior start of study drug. An erythroid stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment.
23. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
24. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 150 days after the last dose of PDR001. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

[redacted]

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

Women are considered post-menopausal and not of child bearing potential if they have had over 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile age appropriate (e.g. generally 40-59 years), history of vasomotor symptoms (e.g. hot flushes) in the absence of other medical justification or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

6 Treatment

6.1 Study treatment

The investigational treatment is PDR001.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
PDR001	Powder for solution for infusion	1 mg/kg (starting dose)	Every 2 weeks (or alternative regimens, e.g. Q3W, Q4W)

PDR001 will be administered via i.v. infusion over 30 minutes (up to 2 hour, if clinically indicated) once every 2 weeks. The next dose may be delayed by up to 7 days to recover from previous AEs (see Section 6.3.2) before receiving the next dose. If the next dose cannot be administered within the above mentioned 7-day delay, then the dose should be skipped. Dosing will resume at the next scheduled dose and assessment schedule will be shifted accordingly. Dose modifications should follow Section 6.3.1 and Section 6.3.2.

If a significant number of patients require dose delays due to PDR001-related toxicities, or if the PK data support it, the dosing regimen for the study may be changed to once every 28 days. This will be discussed in a dose escalation teleconference at the time of the proposed change and documented in the meeting minutes accordingly (see Section 6.2.3). Alternative dosing regimens may also be considered based on clinical toxicity and preliminary PK/PD and efficacy findings.

Once the RP2D dose and schedule are determined, patients from the dose escalation who have completed 4 cycles of treatment may be offered the option of switching to the RP2D (dose and schedule). If this change leads to an increase in the dose, then the patient must fulfill the criteria outlined in Section 6.2.3.4 for intrapatient dose escalation.

6.1.2 Ancillary treatments

Patients should not receive pre-medication to prevent infusion reaction before the first infusion of PDR001, in order to determine if pre-medication is necessary. If a patient experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-

[redacted]

medication should be chosen per institutional standard of care, at the discretion of the treating physician.

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

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

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

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

6.1.3 Treatment duration

A patient may continue treatment with PDR001 until the patient experiences unacceptable toxicity, confirmed disease progression per irRC and/or treatment is discontinued at the discretion of the investigator or the patient. Patients will not be withdrawn from the study due to progressive disease per RECIST. Refer to Section 7.1.4 and Section 7.1.6.

If more than 2 consecutive doses of PDR001 have to be skipped due to PDR001-related toxicities, then the drug should be permanently discontinued. If a patient who misses more than 2 consecutive doses due to a PDR001-related toxicity is experiencing clinical benefit, and in the opinion of the investigator it is in the patient's best interest to remain on study, then the patient may continue treatment after discussion with Novartis.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

PDR001 cross reacts with monkey PD-1 but not rodent PD-1; therefore, the starting dose selected for this study is based on 4-week GLP toxicology studies performed in cynomolgus monkeys. PDR001 is a naked monoclonal antibody that does not have agonist activity, and will be administered to patients with advanced malignancies; therefore the starting dose is based on the ICH S9 guidance. The HNSTD was 100 mg/kg, administered i.v., once weekly. As PDR001 will be administered i.v. and it is generally accepted that antibody therapeutics allometrically scale according to body weight, the human equivalent dose (HED) of the HNSTD is 100 mg/kg. The maximum permitted starting dose in patients is 1/6 x 100 mg/kg, or 17 mg/kg administered weekly. Based on the prior clinical experience with nivolumab and pembrolizumab (Topalian 2012, Topalian 2014, Hamid 2013b, Robert 2014), and with the reasonable assumption that PDR001 will have similar PK/PD properties as those comparators, PDR001 is expected to demonstrate antitumor activity at doses of 2-3 mg/kg dosed every 2-3 weeks. In order to evaluate the safety, PK and antitumor activity of PDR001 across a range of doses, the

[redacted]

recommended starting dose in this study will be 1 mg/kg, i.v., every 2 weeks, which is well below the maximum permitted starting dose.

6.2.2 Provisional dose levels

Table 6-2 describes the starting dose and the dose levels that may be evaluated during this trial.

Table 6-2 Provisional dose levels

Dose level	Proposed dose*	Increment from previous dose
-1**	0.3 mg/kg	-70%
1**	1 mg/kg	Starting dose
2	3 mg/kg	300%
3	10 mg/kg	333%

*It is possible for additional and/or intermediate dose levels to be added during the course of the study Cohorts may be added at any dose level below the MTD in order to better understand safety, PK or PD. Multiple dose levels below the MTD may be evaluated simultaneously in order to obtain PK and PD data across a range of doses and to establish the RP2D.
**Dose level -1 represents a treatment dose for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study.

6.2.3 Guidelines for dose escalation and determination of MTD or RP2D

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified dose level. The first cohort will be treated with the starting dose of 1 mg/kg.

Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions (Section 10.1.4). Also, for the dose-exposure analysis, patients must have received at least one dose of PDR001 during Cycle 1 and have sufficient PK samples in cycle 3 to evaluate the $AUC_{(0\text{-}336h)}$ (Section 10.1.5). Dose escalation decisions will occur when the cohort of patients has met these criteria. If only 2 patients in a cohort are evaluable and neither patient has experienced a treatment-related toxicity > CTCAE grade 1, dose escalation decisions may be considered.

Dose escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data during Cycle 1, and available PK, including Bayesian dose-exposure modeling, and PD data from evaluable patients. The recommended dose for the next cohort of patients will be guided by the Bayesian linear model and the BLRM with EWOC principle evaluating the probability of DLT (Section 10.4.2).

[redacted]

6.2.3.1 Bayesian dose-exposure model

The Bayesian linear model will estimate the dose-exposure relationship for PDR001 in order to guide the dose recommendation. The pharmacokinetic profiles of pembrolizumab and

[redacted]

nivolumab are similar, as expected considering that both are naked monoclonal antibodies that bind to the same target (Patnaik 2012, Robert 2014, Brahmer 2012), and the pharmacokinetic profile of PDR001 is expected to be similar. Based on the exposure data reported for pembrolizumab and nivolumab at their approved doses of 2 mg/kg and 3 mg/kg, respectively (pembrolizumab US label; nivolumab US label), a PDR001 $AUC_{(0\text{-}336h)} \geq 1000$ µg*day/mL at cycle 3 is expected to provide antitumor activity comparable to that of pembrolizumab and nivolumab.

A Bayesian linear model will be used to estimate the dose-exposure relationship for PDR001 in order to guide the dose recommendation to achieve a PDR001 $AUC_{(0\text{-}336h)} \geq 1000$ µg*day/mL in cycle 3, as described in Section 14.3.1.4. The dose-exposure relationship will be evaluated only when sufficient exposure data are available.

6.2.3.2 Bayesian logistic regression model of DLT rate

The adaptive Bayesian methodology provides an estimate of DLT rate for all dose levels of PDR001 that do not exceed the MTD and incorporates all accumulated DLT information from all dose cohorts for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval [16-33%) and will always satisfy the EWOC principle (less than 25% probability that the DLT rate is ≥ 33%). In all cases, the dose for the next cohort will not exceed a 334% (1/2 log) increase from the previous dose. Smaller increases in dose may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data.

If the first 2 patients in a cohort experience a DLT, further enrollment to that cohort will stop and the BLRM will be updated with this new information. Re-evaluation of the available safety, PK, and PD data will occur. By incorporating information gained at the preceding dose levels, additional patients may be enrolled at this dose level or a lower dose level as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk that this dose exceeds the MTD remains below 25% (EWOC).

Dose escalation will continue until identification of the RP2D, which is expected to occur before the MTD is reached. However, dose escalation will stop when the MTD is reached, even if the exposure criteria for the RP2D have not been met.

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

1. at least 6 patients have been treated at this dose
2. this dose satisfies one of the following conditions:
   a. the posterior probability of targeted toxicity at this dose exceeds 25% and is the highest among potential doses, or
   b. minimum of 21 patients have already been treated on the trial to identify the MTD. Recommendation of RP2D may be made with fewer patients, prior to identification of MTD.
3. it is the maximum dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference see Section 6.2.3.3.

[redacted]

To better understand the safety, tolerability and PK of PDR001, additional cohorts of patients may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation. Multiple dose levels may be evaluated in simultaneous cohorts, as long as none exceeds the maximum dose permitted by the BLRM, and a maximum of 6 patients are treated at a dose level greater than the highest dose previously shown to be safe. Depending on the $AUC_{(0\text{-}336h)}$ and predicted DLT rate, it is possible that the dose will not be escalated above the starting dose of 1 mg/kg, and it is possible that doses greater than required to achieve the target exposure will be explored as long as they do not exceed the maximum dose permitted by the BLRM.

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

6.2.3.3 Implementation of dose escalation decisions

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

6.2.3.4 Intra-patient dose escalation

For patients enrolled in the Phase I part of the study, intra-patient dose escalation is not permitted at any time within the first 4 cycles of treatment. After cycle 4 is completed, individual patients may be considered for treatment at a dose of PDR001 higher than the dose to which they were initially assigned and/or a different dosing regimen. In order for a patient to be treated at a higher dose of PDR001, he or she must have tolerated the lower dose for at least 4 cycles of therapy (i.e. he or she must not have experienced any PDR001-related toxicity CTCAE grade ≥ 2 at the lower dose originally assigned). Moreover, the new, higher dose with which the patient is to be treated must be a dose that has completed evaluation and has not exceeded the maximum tolerated dose (MTD). There is no limit to the number of times a patient may have his or her dose of PDR001 increased. For any further increase after the initial intra-patient dose escalation, the following rules apply: the patient must have experienced no CTCAE grade ≥ 2, PDR001-related toxicity over at least two cycles of therapy at the lower dose, and the higher dose being considered must have been fully evaluated and shown not to exceed the MTD. Consultation and agreement with Novartis must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record eCRF. Data from the first cycle of treatment at the new dose level will not be formally included in the statistical model describing the relationship between dose and occurrence of DLT. However, these data will be incorporated into the clinical assessment of safety during dose escalation teleconferences.

[redacted]

For patients enrolled in the phase II part of the study, intra-patient dose escalation or change in dosing regimen is not permitted.

6.2.4 Definitions of dose limiting toxicities (DLTs)

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

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

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

Table 6-3 Criteria for defining dose limiting toxicities

DLTs include any AE of CTCAE grade 3 or higher occurring in cycle 1, during the dose escalation part of the study, for which relationship to study treatment cannot be ruled out, with the following exceptions:	
Hematology	Neutropenia is a DLT if it is CTCAE grade 4. Thrombocytopenia is a DLT if it is CTCAE grade 4. Anemia is a DLT if it is CTCAE grade 4. Lymphopenia is a DLT if it is CTCAE grade 4.
Hepatic	≥ CTCAE grade 2 total bilirubin with ≥ CTCAE grade 2 ALT is a DLT.
Gastrointestinal	Nausea and vomiting are DLTs if they are ≥ CTCAE grade 3 for > 2 days despite optimal anti-emetic therapy. Diarrhea is a DLT if it is ≥ CTCAE grade 3 for > 2 days despite optimal anti-diarrhea treatment.
Pneumonitis	CTCAE grade 2 pneumonitis is a DLT if it persists > 7 days despite treatment with corticosteroids. Grade 3-4 pneumonitis of any duration is a DLT.
Hypertension	CTCAE grade 3 hypertension is a DLT if it persists > 7 days despite treatment. Grade 4 hypertension of any duration is a DLT.
Infection	CTCAE grade 3 infection or fever in the absence of neutropenia are DLTs if they persist > 5 days. Grade 4 infection of any duration is a DLT.
Electrolytes	CTCAE grade 3 electrolyte abnormalities are DLTs if they persist > 7 days despite treatment or are clinically significant. Grade 4 electrolyte abnormality of any duration is a DLT.
Rash and/or photosensitivity	≥ CTCAE grade 3 rash or photosensitivity are DLTs if they persist > 7 days despite treatment.
Fatigue	Fatigue is a DLT if it is ≥ CTCAE grade 3 and lasts > 7 days.
Immune related toxicities (except pneumonitis)	CTCAE grade 3 immune related toxicities are DLTs if they persist > 7 days despite treatment with corticosteroids. Immune related toxicities CTCAE grade 4 of any duration are DLTs.
Other AEs	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in cycle 1, may be considered to be DLTs by the Investigators and Novartis, even if not CTCAE grade 3 or higher.

[redacted]

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose or schedule adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied:

- For clinical management of suspected immune-related events, reference to consensus management guidelines is recommended such as those provided in the National Comprehensive Cancer Network (NCCN) Guidelines for the Management of Immunotherapy-Related Toxicities (available at: nccn.org/professionals/physician_gls/default.aspx#immunotherapy), the American Society of Clinical Oncology clinical practice guideline for Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy (Brahmer 2018) or the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Management of Toxicities from Immunotherapy (Haanen 2017). Note that in general, study treatment should be interrupted for grade 3 and 4 toxicities and for a subset of lower grade toxicities.
- Consider early referral to specialists with expertise in the diagnosis and management of immune-related AEs to thoroughly investigate events of uncertain etiology.
- Events not included in the study protocol or the reference guidance documents should be managed per institutional preference.
- A decision to resume treatment following the occurrence of a DLT, grade 3 or 4 or serious adverse suspected immune-related events that occur after the DLT period may be taken only after documented discussion with the Novartis medical monitor.

If more than 2 consecutive doses have to be skipped due to PDR001-related toxicities, then the patient must be discontinued from the study treatment. If a patient who misses more than 2 consecutive doses due to a PDR001-related toxicity is experiencing clinical benefit, and in the opinion of the investigator it is in the patient's best interest to remain on study, then the patient may continue treatment after discussion with Novartis.

Patients who discontinue the study for a study related AE or a study-related abnormal laboratory value must be followed as described in Section 6.3.2.

All interruptions or change to study drug administration must be recorded on the Dose Administration Record eCRF.

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. In case of a suspected autoimmune disease AE, the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed. In case of a toxicity suspected to be a cytokine release syndrome, the assessments outlined in Section 7.2.2.5.6 must be performed. All patients

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must be followed up for AEs and SAEs for 150 days following the last dose of PDR001. Table 6-4 outlines the follow-up evaluation recommended for selected toxicities.

Table 6-4 Follow-up evaluations for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION AND TREATMENT RECOMMENDATIONS
Infusion Reaction or hypersensitivity reaction	
Grade 1	Decrease infusion rate until recovery of the symptoms.
Grade 2	Stop infusion immediately, and keep line open. Follow institutional guidelines for the management and follow-up of infusion reaction. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then permanently discontinue study treatment.
Grades 3 and 4	Discontinue infusion immediately, and discontinue study treatment. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (e.g., blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.
Cytokine Release Syndrome (CRS)	
Grade 2	See instructions for Grade 2 Infusion Reaction above.
Grade 3 or Grade 4	Discontinue study treatment. Follow-up CRS as per institutional guidelines. Take blood for cytokine measurements as specified in Section 7.2.2.5 Laboratory evaluations
Ocular (uveitis, eye pain, blurred vision)	
Grade 1	Continue study treatment without dose modification. Ophthalmology consultation.
Grade 2	Hold study treatment. Urgent ophthalmology consultation. Upon resolution to ≤ Grade 1 may consider resuming study treatment without dose reduction after discussion with the Novartis Medical Monitor and in consultation with ophthalmology.
Grade 3 or Grade 4	Discontinue study treatment. Urgent ophthalmology consultation.
Pulmonary (Pneumonitis)	
Grade 1	Consider study treatment hold. Manage per institutional practice. Consider resuming study treatment upon radiographic evidence of improvement.
Grade 2	Hold study treatment. Pulmonary and infection workup. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification.
Grades 3 and 4	Discontinue study treatment.
Cardiovascular **ECG QTc-Interval prolonged; hypertension**	
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline (hypertension, QTc) or < 30 msec difference from baseline (QTc) within ≤ 7 days, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor. Baseline ECG refers to ECG(s) collected at screening.
Grade 4	Discontinue study treatment.

[redacted]

TOXICITY	FOLLOW-UP EVALUATION AND TREATMENT RECOMMENDATIONS
Other cardiovascular disorders	
Grade 2 (except myocarditis)	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 2 myocarditis, or Grade ≥ 3 other cardiac disorders related to study treatment	Discontinue study treatment.
Gastrointestinal	
Diarrhea/colitis*	
Grade 1	May continue study treatment without dose modification. Manage per institutional standard guidelines which could include anti-diarrheal treatment, consideration of corticosteroid therapy, and hydration.
Grade 2	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade3	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 4	Discontinue study treatment.
AST and/or ALT elevation	
Grade 2 AST and/or ALT	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1 or baseline, consider resuming study treatment without dose modification.
Grade 2 transaminitis with bilirubin > 1.5 X ULN (unless Gilbert's syndrome)	Discontinue study treatment.
Grade 3 AST and/or ALT	Hold study treatment. Manage per institutional practices. Upon resolution to ≤ Grade 1 or baseline within 7 days, consider resuming study treatment without dose modification after discussion with the Novartis Medical Monitor. Otherwise, discontinue study treatment.
Grade 4 AST and/or ALT	Discontinue study treatment.
Isolated total bilirubin elevation**	
Grade 2	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, may continue study treatment without dose modification.
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, may consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 4	See footnote **. Otherwise, discontinue study treatment.

[redacted]

TOXICITY	FOLLOW-UP EVALUATION AND TREATMENT RECOMMENDATIONS
Asymptomatic amylase and/or lipase elevation * **	
Grade 3 or Grade 4, not associated with symptoms or clinical manifestations of pancreatitis***	Continue study treatment. If levels do not resolve to ≤ Grade 2 within ≤ 14 days after the initial report, hold study treatment. Upon resolution to ≤ Grade 2, may resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Pancreatitis	
Grade 2/radiologic evidence	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification, if no clinical evidence of pancreatitis and after discussion with the Novartis Medical Monitor.
Grades 3 or Grade 4	Discontinue study treatment.
Renal	
Serum creatinine	
Grade 2	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 3 or 4	Discontinue study treatment.
Musculoskeletal	
Grade 2 or Grade 3	Hold study treatment. Consider resuming study treatment without dose modification upon resolution to ≤ Grade 1 with appropriate management.
Grade 4	Discontinue study treatment. In some cases, resuming study treatment may be considered after discussion with the Novartis Medical Monitor and consultation with a rheumatologist.
Endocrine	
Hypothyroidism or hyperthyroidism	
Grade 2	May continue study treatment without dose modification. Management according to institutional practice.
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 4	May resume therapy following resolution or control with physiologic hormone replacement.
Other endocrine disorders	
Grade 2 and Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 4	Hold study treatment. Grade 4 treatment-related endocrinopathies, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Novartis Medical Monitor.
Neurology	
Grade 1	Consider study treatment hold, particularly for clinical suspicion of Guillain-Barre syndrome, encephalitis, aseptic meningitis, transverse myelitis, or peripheral neuropathy.
Grade 2	Hold study treatment. In some cases, resuming study treatment may be considered after discussion with the Novartis Medical Monitor.

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TOXICITY	FOLLOW-UP EVALUATION AND TREATMENT RECOMMENDATIONS
Grade 3 or Grade 4	Discontinue study treatment.
Dermatology (rash)	
Grade 1	Continue study treatment without dose modification. Topical steroids, antihistamines, topical emollients.
Grade 2	Consider holding study treatment. Topical or oral steroids, antihistamines. If study treatment is held and resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 3 or Grade 4	Hold study treatment. Manage per institutional practice. After resolution to ≤ Grade 1, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Bullous dermatitis	Hold study treatment. Grade 1-2 bullous dermatitis: discussion with the Novartis Medical Monitor is required before considering resuming study treatment. Grade 3 bullous dermatitis: consider resuming therapy after expert consultation and documented discussion with the Novartis medical monitor. Grade 4 bullous dermatitis: discontinue study treatment.
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue study treatment.
Hematology	
Neutropenia (ANC)	
Grade 3 or Grade 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Febrile neutropenia	
Grade 3 or Grade 4	Hold study treatment. Upon resolution of fever and improvement of neutropenia to ≤ Grade 2 or baseline, resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Thrombocytopenia	
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline, resume study treatment without dose modification. For Grade 3 associated with major bleeding, discontinue study treatment.
Grade 4	Discontinue study treatment.
Anemia	
Grade 3 or Grade 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within 7 days, resume study treatment without dose modification.
Lymphopenia	
Any grade	Treatment-related lymphopenia does not require study treatment hold or discontinuation.
Other laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1, resume study treatment without dose modification.

[redacted]

TOXICITY	FOLLOW-UP EVALUATION AND TREATMENT RECOMMENDATIONS
Grade 4	Isolated Grade 4 electrolyte abnormalities not associated with clinical sequelae and corrected after appropriate management within 72 hours of their onset do not require discontinuation. In the case of Grade 4 electrolyte imbalances associated with clinical sequelae, or not resolved to ≤ Grade 1 within 72 hours despite appropriate management, discontinue study treatment.
Other non-laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 2	Consider study treatment hold, at Investigator discretion. Upon resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1, resuming study treatment must be discussed with the Novartis Medical Monitor.
Grade 4	Discontinue study treatment.
All dose modifications should be based on the worst preceding toxicity. *Note: anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea. **Note: If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then delay study treatment until resolved ≤ Grade 1, and resume study treatment at the discretion of the investigator. ***Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within one week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase.	

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, i.e. infusion reaction, pneumonitis and other immune related toxicities, are provided in Section 6.3.2. Refer to preclinical toxicity data provided in the [Investigator's Brochure].

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

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

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

6.4.2 Permitted concomitant therapy requiring caution and/or action

Treatment with hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) may not be initiated during the first cycle in the dose escalation part of the study, unless

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the patient has already experienced a DLT. Treatment with erythroid stimulating agents (ESAs) may not be initiated during the first cycle in the dose escalation part of the study, unless the patient has already experienced a DLT. If a patient is using ESA prior to enrollment (at least 2 weeks before start of study treatment), they may continue at the same dose.

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

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

6.4.3 Prohibited concomitant therapy

During the course of the study, patients may not receive other additional investigational drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. However, limited-field palliative radiotherapy to non-target lesion(s) may be allowed as concomitant therapy after documented discussion with Novartis. For patients with anaplastic thyroid cancer, limited-field radiotherapy to a target lesion that is life-threatening may be allowed, provided that other measurable disease remains to allow an assessment of response to treatment. These cases must be discussed with Novartis with written permission. Such local therapies administered during the study treatment must be listed on the Concomitant Antineoplastic Therapy – Radiotherapy CRF.

After progression of disease as per RECIST criteria, radiotherapy and surgery to select target and non-target lesion(s) (such as brain metastases) may be allowed as concomitant therapy after documented discussion and approval by Novartis.

Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication may be administered while on this study.

The use of systemic steroid therapy is not allowed, except for the treatment of the following: infusion reactions, immune-mediated toxicities (patients may resume study treatment while on tapering with doses $\leq$ 10 mg/day prednisone or equivalent), COPD exacerbation and replacement-dose steroids in the setting of adrenal insufficiency. Additional exceptions may be discussed with Novartis. Topical, inhaled, nasal and ophthalmic steroids are not prohibited.

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

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first pre-screened (if applicable) or when the patient is enrolled for screening. The subject number is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as

assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition page.

6.5.2 Treatment assignment or randomization

The assignment of a patient to a particular cohort will be coordinated by the sponsor. No randomization will be performed in this study.

6.6 Study drug preparation and dispensation

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

All dosages prescribed to the patient, all dose interruptions and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.6.1 Study drug packaging and labeling

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

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but will not supply information about the patient.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, PDR001 should be stored according to the instructions specified on the drug labels.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

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

[redacted]

6.6.3.2 Study drug accountability

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

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table ("Category" column) indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S).

No CRF will be used as a source document.

Screening/baseline evaluations must be performed ≤ 21 days of Cycle 1 Day 1, except for baseline radiological evaluations which must be done within 28 days and pregnancy test which is to be performed within 3 days prior to the first dose of study treatment. Assessments performed as part of the screening evaluations and within 3 days prior to the first dose of study treatment, are not required to be repeated on the first dosing day. Laboratory and radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within the screening time window.

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

Radiological assessments must be performed +/- 1 week of the scheduled date of the assessment.

[redacted]

Table 7-1 Visit evaluation schedule (applicable for all treatment regimens, duration of cycle is adapted accordingly)

			Screening Phase		Treatment Phase																	Follow-up		
Visit name	**Category**	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**							**Cycle 2**		**Cycle 3**							**Subsequent cycles**	**EoT**	**Safety F/U[4]**	**Disease Progression F/U**	**Survival F/U**
Day of cycle				-21 to -1	1	2	3	4	8	11	15	1	15	1	2	3	4	8	11	15	1				
Obtain molecular pre-screening Informed Consent	D	7.1.1.	X[7]																						
Obtain Informed Consent	D	7.1.2.		X																					
[redacted]																									
Demography	D	7.1.2.2.	X	X																					
Inclusion/ exclusion criteria	D	5.2 and 5.3.		X																					
Medical History	D	7.1.2.2.		X																					
Diagnosis and extent of cancer	D	7.1.2.2.		X																					
EBV and MSI status (if applicable)	D	7.1.2.2.		X																					
EGFR, ALK, BRAF V600 status (if applicable)	D	7.1.2.2.	X																						
Prior antineoplastic therapy	D	7.1.2.2.		X																					
Prior/concomitant medications and non-drug procedures	D	7.1.2.2 and 6.4.		X	Continuous[4]																				
[redacted]																									

			Screening Phase		Treatment Phase																	Follow-up		
Visit name	**Category**	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**							**Cycle 2**		**Cycle 3**							**Subsequent cycles**	**EoT**	**Safety F/U[4]**	**Disease Progression F/U**	**Survival F/U**
Day of cycle				-21 to -1	1	2	3	4	8	11	15	1	15	1	2	3	4	8	11	15	1				
Concomitant antineoplastic radiotherapy	D	6.4.3.			Continuous																			
Physical examination	S	7.2.2.1.		X	X				X		X	X	X	X							X	X			
Height	D	7.2.2.3.		X																					
Weight	D	7.2.2.3.		X	X							X		X							X	X			
Vital signs	D	7.2.2.2.		X	X				X		X	X	X	X							X	X			
Performance status	D	7.2.2.4.		X																					
Hematology	D	7.2.2.5.1.		X	X				X		X	X	X	X							X	X			
Chemistry	D	7.2.2.5.2.		X	X				X		X	X	X	X							X	X			
Coagulation	D	7.2.2.5.3.		X																					
Urinalysis	D	7.2.2.5.4.		X																					
Thyroid function	D	7.2.2.5.5.		X	X							X		X							X	X			
Cytokines (IFN-γ; IL-6)	D	7.2.2.5.6.		X	In case of a suspected cytokine release syndrome																			
Pregnancy test	D	7.2.2.5.7.		X								X		X							X	X			
	S																						X[4]		
HBV, HCV & HIV	D	7.2.2.5.8.		X																					
Antineoplastic therapies since discontinuation of study treatment	D	7.1.6.																					X	X	X

[redacted]

			Screening Phase		Treatment Phase																	Follow-up		
Visit name	**Category**	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**							**Cycle 2**		**Cycle 3**							**Subsequent cycles**	**EoT**	**Safety F/U[4]**	**Disease Progression F/U**	**Survival F/U**
Day of cycle				-21 to -1	1	2	3	4	8	11	15	1	15	1	2	3	4	8	11	15	1				
Tumor evaluation as per RECIST 1.1 and as per irRC.	D	7.2.1.		X	Every 8 weeks ± 1 week from 8 weeks post Cycle 1 Day 1 up to 40 weeks, then every 12 weeks ± 1 week until progression of disease per irRC or patient withdrawal. For disease progression f/u, every 8 weeks ± 1 week until 40 weeks, then every 12 weeks± 1 week until progression of disease per irRC, withdrawal of consent, or lost to follow-up.																			
ECG	D	7.2.2.6.1.		X	As clinically indicated																			
Adverse events	D	8.	X[6]	Continuous																				
[redacted]																								
Collection of archival tumor sample	D	7.2.4.	X, if needed	X, if not collected at molecular pre-screening																				
Collection of newly obtained tumor sample	D	7.2.4.	X, if needed	X, if not collected at molecular pre-screening										X[2]										
[redacted]																								

			Screening Phase		Treatment Phase																	Follow-up		
Visit name	**Category**	**Protocol Section**	**Molecular Pre-screening**	**Screening**	**Cycle 1**							**Cycle 2**		**Cycle 3**							**Subsequent cycles**	**EoT**	**Safety F/U[4]**	**Disease Progression F/U**	**Survival F/U**
Day of cycle				-21 to -1	1	2	3	4	8	11	15	1	15	1	2	3	4	8	11	15	1				
Collection of newly obtained tumor sample	D	7.2.4.			Optional sample collected upon disease progression, for patients who had a response to treatment (as determined by the investigator).																				
Study Drug administration	D	6.1.1.			i.v. every 2 weeks (potential alternative schedule, e.g. every 3 or 4 weeks).																				
PK sampling	D	7.2.3.			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X[1]	X	X[8]		
Immunogenicity (IG) sampling	D	7.2.3.			X							X		X							X[1]	X			
[redacted]																									
Survival contact	D	7.1.6.																							X

[1] Cycles 4-6 only.
[2] Anytime from Cycle 3 Day 1 through Cycle 3 Day 15.
[3] Cycle 6 Day 1 only.
[4] Safety evaluations for 150 days after the last dose of study treatment with contacts at 30-, 90-, and 150-day. After initiation of new antineoplastic therapy, only AEs/SAEs **suspected** to be related to study treatment will be collected. Pregnancy tests every month until the 150-day safety follow-up; can be performed at home or at a local doctor's office if the patient is not coming to the clinic. Concomitant medications collected until the 30-day safety follow-up or the start of new antineoplastic therapy, whatever occurs first.
[5] If the reason for discontinuation is disease progression and a sample at C1D1 was collected.
[6] To collect only the molecular pre-screening Procedure Related SAEs.
[7] if written documentation of EGFR (for NSCLC indication), ALK (for NSCLC indication if negative for EGFR mutation) or BRAF V600 mutation (for melanoma indication) is unavailable.
[redacted]

[redacted]

7.1.1 Molecular pre-screening

Patients, for whom the required mutational status was not already assessed outside of this study, must sign the molecular pre-screening informed consent and provide a new tumor biopsy sample (or archival biopsy sample if new biopsy is not possible), which will be locally analyzed for mutational status or by a Novartis-designated laboratory if a local laboratory test is not feasible. Once the mutational status is confirmed by the laboratory and documented by the site, the patient may begin the screening procedures.

The molecular pre-screening informed consent must be signed prior to any study-related molecular pre-screening procedure.

To enter the screening phase of this study, patients must complete the molecular pre-screening assessment if written documentation of EGFR (for NSCLC indication), ALK (for NSCLC indication if negative for EGFR mutation) or BRAF V600 mutation (for melanoma indication) is unavailable. EGFR mutation-negative is defined as negative for exon 19 deletions and for the L858R mutation in EGFR at a minimum; however, if more extensive EGFR mutation testing has been performed, the tumor must not harbor any known activating EGFR mutations in Exons 18-21 in order to be considered EGFR mutation-negative.

7.1.2 Screening

The study IRB/IEC approved informed consent form must be signed and dated before any screening procedures are performed, except for laboratory and radiological evaluations performed as part of standard of care within the screening window.

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

7.1.2.1 Information to be collected on screening failures

Patients who sign the molecular pre-screening informed consent and/or the main study informed consent, but fail to be started on study treatment for any reason will be considered as screen failure and data will be handled in the same manner.

The screening failure will be entered on the Screening Phase Disposition Page.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during screening (see Section 8.2 for SAE reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported (i.e., tumor biopsy).

7.1.2.2 Patient demographics and other baseline characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, diagnosis and extent of tumor, details of prior anti-neoplastic treatments, prior medication, procedures, significant non-drug therapies and any other assessments that are done for the purpose of determining eligibility for inclusion in the study.

[redacted]

For patients with breast cancer, ER, PR and HER2 status will be collected. For patients with Gastric cancer and esophageal adenocarcinoma, the MSI status and the EBV status will be collected. For patients with CRC, the MSI status will be collected. If the EBV or the MSI status determination is not performed routinely as part of the patient standard follow-up, they will need to be determined locally during screening. In the phase II part of the study, for patients with NSCLC, the EGFR and ALK mutation status will be collected; for patients with melanoma, the BRAF V600 mutation status will be collected. Patients must not have a tumor with a mutation on these markers to be eligible, but the status of these markers must be known to determine the eligibility of the patient (Section 5.2). For patients with anaplastic thyroid cancer, BRAF V600 mutation status will be collected but is not required to determine eligibility to the study.

Therefore, if the EGFR, ALK (if applicable) or BRAF V600 status is not known, it will need to be determined at molecular pre-screening as applicable at a local laboratory, or by a Novartis-designated laboratory if a local laboratory test is not feasible.

7.1.3 Treatment period

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

Patients will be treated until they experience unacceptable toxicity, progressive disease per irRC and/or treatment is discontinued at the discretion of the investigator or the patient, as described in Section 7.1.4 and Section 4.3. Patients should not discontinue treatment based on progressive disease per RECIST.

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

7.1.4 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

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

Study treatment may be discontinued if any of the following occur:

- Adverse event
- Lost to follow-up

[redacted]

- Physician's decision
- Progressive disease per irRC (not per RECIST)
- Study terminated by the sponsor
- Subject/guardian decision
- Protocol deviation
- Technical problems

Study treatment must be discontinued if any of the following occur:

- Death
- Pregnancy

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, and within 14 days of the last dose of study drug or within 14 days of the decision to permanently discontinue study treatment, at which time all of the assessments listed for the EOT visit will be performed (Table 7-1). If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit. An End of Treatment Phase Disposition CRF page should be completed, giving the date and reason for stopping the study treatment. End of treatment/Premature withdrawal visit is not considered as the end of the study.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.1.6. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.7. If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments.

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

7.1.4.1 Replacement policy

Phase I dose escalation part:

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

Phase II expansion part:

During the phase II expansion part no replacements will be needed.

[redacted]

7.1.5 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore,
- Does not allow further collection of personal data.

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

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

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

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

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of the withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.6 Follow up period

All patients must have safety evaluations for 150 days after the last dose of study treatment. The evaluations can be done either by telephone call or visit for the 30-, 90-, and 150-day safety follow-up visits. Concomitant medications will be collected until the 30-day safety follow-up has been completed or the start of new antineoplastic therapy, whichever occurs first. If the 150-day safety evaluation is conducted by phone, samples do not need to be collected. Data collected should be added to the Adverse Events CRF, the antineoplastic therapies since discontinuation of study treatment CRF, the Concomitant Medications CRF, Biomarker blood sample CRF, and PK[redacted] CRFs. For PK[redacted] samples and Biomarker samples collection schedule is outlined in Section 7.2.3 and Section 7.2.4 respectively. For female patients of child bearing potential, pregnancy tests will be performed as outlined in Section 7.2.2.5.7.

Patients who discontinue study treatment for any reason other than death, disease progression per irRC, clinical progression, lost to follow-up, consent withdrawal, start of new cancer therapy or study termination, also should return for tumor evaluation assessments and should not be considered withdrawn from the study until 80% of the patients in each disease group of the

[redacted]

phase II part have had progression of disease or discontinued the study for any reason. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient had disease progression. Once the Follow up for Disease progression period ended, the End of Post treatment Phase disposition CRF should be completed.

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

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

For patients who transfer to another clinical study or an alternative treatment option to continue provision of study treatment, as described in Section 4.3, the follow-up for 150-day safety, disease progression and survival will not be performed.

7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be determined locally according to two sets of criteria:

1. RECIST v1.1 (Appendix 1)
2. irRC (Appendix 2)

The local investigator's assessment will be used for the analysis of response according to both RECIST 1.1 and irRC, and for treatment decision making (study discontinuation due to PD as per irRC). During the course of the study, Novartis may decide to have a central review of the radiological assessments performed. In such case, the investigator's staff will be instructed on how to send data from these radiological assessments to a Contract Research Organization (CRO) for central review when needed.

At screening, all patients will undergo CT with i.v. contrast of the chest, abdomen and pelvis. If there is clinical evidence of disease in the neck, a CT with i.v. contrast of the neck will also be performed. MRI should only be used to evaluate sites of disease that are not adequately imaged by CT. If a patient is intolerant of iodine-based contrast agents, CTs may be performed without contrast. MRI may be used to evaluate sites of disease where a CT without i.v. contrast is not adequate. Visible skin lesions and easily palpable subcutaneous tumors may be measured

[redacted]

by physical examination using a ruler or calipers. Ultrasound should not be used to measure sites of disease. See Table 7-2 for further details.

Tumor assessments will be performed at the following time points:

- Screening
- Every 8 weeks ± 1 week from 8 weeks post Cycle 1 Day 1 up to 40 weeks, then every 12 weeks ± 1 week until progression of disease per irRC or patient withdrawal. After EOT, during disease progression f/u, every 8 weeks ± 1 week until 40 weeks, then every 12 weeks ± 1 week until progression of disease per irRC, withdrawal of consent or lost to follow-up.
- PR or CR, per both RECIST 1.1 and irRC, will be confirmed by a new assessment after at least 4 weeks. Also PD, as per irRC, will be confirmed after at least 4 weeks.
- At the End of Treatment, if a scan was not conducted within 30 days prior to End of Treatment

Disease progression follow-up should be performed as described in Section 7.1.6.

Table 7-2 Disease assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI **with contrast enhancement** (Chest, Abdomen, Pelvis)	Mandated	During treatment, before EOT: Every 8 weeks ± 1 week until completion of 40 weeks, then every 12 weeks ± 1 week until progression of disease per irRC or patient withdrawal. After EOT, during disease progression f/u, every 8 weeks ± 1 week until 40 weeks, then every 12 weeks ± 1 week until progression of disease per irRC, withdrawal of consent or lost to follow-up.
Brain CT or MRI with contrast	For patients with known CNS metastases, or if clinically indicated	For patients with known CNS metastases, or if clinically indicated
Whole body bone scan	If clinically indicated	If clinically indicated
Localized bone CT, MRI or x-ray	For any lesions identified on the bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Any other procedure allowed as per RECIST 1.1 guidelines (Section 14.1)		

7.2.2 Safety and tolerability assessments

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

7.2.2.1 Physical examination

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

At Screening and Cycle 1 Day 1, prior to PDR001 infusion, a complete physical examination will be performed and will include the examination of general appearance, skin, neck (including

[redacted]

thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

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

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

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before dosing and as indicated in Table 7-1.

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

7.2.2.3 Height and weight

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

7.2.2.4 Performance status

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

Table 7-3 ECOG performance status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

7.2.2.5 Laboratory evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally. Refer to Table 7-4 for a summary of the parameters to be evaluated according to Table 7-1. On days of PDR001 dosing, samples for these parameters will be collected prior to the infusion of PDR001.

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

Novartis will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. In addition, if at any time a patient has laboratory

[redacted]

parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Table 7-4 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Sodium, Potassium, Creatinine, Glucose Magnesium, Inorganic Phosphate, Total Bilirubin (also measure direct and indirect bilirubin if total bilirubin is > grade 1), Blood Urea Nitrogen (BUN) or Urea
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]), activated partial thromboplastin time (APTT)
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific Gravity, White Blood Cells)
Thyroid	Free T4, TSH
Cytokines	IFN-γ; IL-6
Virology	HBV, HCV, HIV

7.2.2.5.1 Hematology

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

7.2.2.5.2 Clinical chemistry

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

7.2.2.5.3 Coagulation

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

7.2.2.5.4 Urinalysis

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

7.2.2.5.5 Thyroid function

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

7.2.2.5.6 Cytokines

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

- Screening

[redacted]

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

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

7.2.2.5.7 Pregnancy and assessments of fertility

Pregnancy tests will be performed for women of child bearing potential.

At screening, a serum pregnancy test must be performed within 3 days before the first dose. During the study (Day 1 of each cycle starting with Cycle 2) a serum or urine pregnancy test must be performed. At End of Treatment, a serum pregnancy test must be performed. A urine pregnancy test should be performed every month during and at the end of the safety follow-up period (i.e. 5 months after the last dose of PDR001). If the patient is not coming to the clinic during the safety follow-up, it can be performed at home or at a local doctor's office, and the results will be communicated to the site staff. These follow-up pregnancy tests will be recorded only in the source documentation, not in the CRF.

7.2.2.5.8 Virology

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

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as per the assessment schedule in Table 7-1 and Table 7-5. Blood samples scheduled at the same time point should be taken after the ECGs are completed. For the Screening only one ECG per visit is required. Unscheduled visits can be either one ECG or in triplicate based on investigator's choice on which is most appropriate.

Table 7-5 12 lead ECG collection plan

Cycle	Day	Time
Screening	-21 to -1	Anytime
Unscheduled	-	Anytime

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

After the first primary CSR cut-off date is reached, ECGs will not be reviewed by the central laboratory.

[redacted]

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

7.2.3 Pharmacokinetic and immunogenicity assessments

The following PK parameters will be determined for PDR001 using non-compartmental methods: Cmax, Tmax, AUC0-tlast (Cycle 1 and Cycle 3), time to last measurable concentration (Tlast), t1/2, and the accumulation ratio of PDR001. Possible relationships between PK and PD variables, efficacy and/or selected toxicities may be explored, as appropriate.

The data will be analyzed using WinNonlin Phoenix (Pharsight Corporation; Mountain View, CA).

PK profiles to assess PK properties of PDR001 will be collected from all enrolled patients. For patients enrolled in the phase I dose escalation part and five patients per disease group 1a, 2, 3 and 4 in the phase II part and 15 patients in disease group 1b in the phase II, the full PK profile will be collected. For all other patients, an alleviated PK sampling schedule is planned. Please refer to Table 7-6 and Table 7-7 for details on PK and IG sample collections.

If the dosing of Cycle 3 Day 1 is delayed, the PK sampling for the full PK profile should be delayed accordingly to match the scheduled time points for cycle 3 as outlined in Table 7-6 and Table 7-7. PK and IG samples will be collected also at the End of Treatment Visit and in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if IG is suspected. After the first primary CSR data cut-off date is reached, no additional PK and IG samples will be collected for the patients still on-going on the study.

[redacted]

[redacted]

[redacted]

Table 7-6 Pharmacokinetic blood collection log [Dose escalation (all patients) and phase II part (5 per disease group (1a, 2, 3 and 4) and 15 patients in group 1b)]

Cycle	Day	Scheduled Time Point (h)**	Analytes	PK Sample No	IG Sample No*
1	1	Predose	mAb, IG [redacted]	1	401
1	1	1h post dose§ (± 5 min)	mAb	2	
1	2	24h post dose (± 2h)	mAb	3	
1	3	48h post dose (± 8h)	mAb	4	
1	4	72h post dose (± 8h)	mAb	5	
1	8	168h post dose (± 8h)	mAb	6	
1	11	240h post dose (± 24h)	mAb	7	
1	15	336h post dose (±24h) (Pre-dose of next dose for Q2W schedule)	mAb	8	
2	1	Predose of cycle 2 (672h ± 48h post dose for Q4W schedule, 504h ± 48h post dose for Q3W schedule)	mAb and IG	9	402
3	1	Predose	mAb, IG [redacted]	101	403
3	1	1h post dose§ (± 5 min)	mAb	102	
3	2	24h post dose (± 2h)	mAb	103	
3	3	48h post dose (± 8h)	mAb	104	
3	4	72h post dose (± 8h)	mAb	105	
3	8	168h post dose (± 8h)	mAb	106	
3	11	240h post dose (± 24h)	mAb	107	
3	15	336h post dose (± 24h) (Pre-dose of next dose for Q2W schedule)	mAb	108	
4	1	Predose of Cycle 4 (672h ± 48h post dose for Q4W schedule, 504h ± 48h post dose for Q3W schedule)	mAb and IG	109	404
5	1	Predose	mAb and IG	201	405
5	1	1h post dose§ (± 5 min)	mAb	202	
6	1	Predose	mAb, IG [redacted]	301	406
6	1	1h post dose§ (± 5 min)	mAb	302	
EOT			mAb and IG	5000	6000
150 days Safety follow-up			mAb [redacted]	X	
Unscheduled			mAb, IG [redacted]	1001+	2001+

*IG [redacted] samples are to be collected together with PK samples at the same time.

§after completion of the infusion.

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

[redacted]

Table 7-7 Abbreviated pharmacokinetic blood collection log [phase II part (all other patients)]

Cycle	Day	Scheduled Time Point (h)**	Analytes	PK Sample No	IG Sample No*
1	1	Predose	mAb, IG [redacted]	1	401
1	1	1h post dose§ (± 5 min)	mAb	2	
1	2	24h post dose (± 2h)	mAb	3	
1	8	168h post dose (± 8h)	mAb	6	
1	15	336h post dose (±24h) (Pre-dose of next dose for Q2W schedule)	mAb	8	
2	1	Predose of cycle 2 (672h ± 48h post dose for Q4W schedule, 504h ± 48h post dose for Q3W schedule)	mAb and IG	9	402
3	1	Predose	mAb, IG [redacted]	101	403
3	1	1h post dose§ (± 5 min)	mAb	102	
3	2	24h post dose (± 2h)	mAb	103	
3	8	168h post dose (± 8h)	mAb	106	
3	15	336h post dose (± 24h) (Pre-dose of next dose for Q2W schedule)	mAb	108	
4	1	Predose of Cycle 4 (672h ± 48h post dose for Q4W schedule, 504h ± 48h post dose for Q3W schedule)	mAb and IG	109	404
5	1	Predose	mAb and IG	201	405
5	1	1h post dose§ (± 5 min)	mAb	202	
6	1	Predose	mAb, IG and RO	301	406
6	1	1h post dose§ (± 5 min)	mAb	302	
EOT			mAb and IG	5000	6000
150 days Safety follow-up			mAb [redacted]	X	
Unscheduled			mAb and IG	1001+	2001+

*IG [redacted] samples are to be collected together with PK samples at the same time.

§after completion of the infusion.

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

7.2.3.1 Bioanalytics

Bioanalysis for pharmacokinetic studies will employ three validated assays:

1. The assay to quantify PDR001 will be a validated LCMS assay.
2. The assay to quantify and assess the IG will be a validated homogeneous ELISA.

[redacted]

7.2.3.2 PK, IG [redacted] samples handling, labeling, and shipping instructions

A total of 4 mL of blood will be collected at each time point. For time points when PDR001 (mAb) PK and IG are to be measured, a single blood sample will be collected for both IG and PDR001 PK. [redacted]
Blood samples should be collected from the arm opposite from the investigational drug infusion, or from another site. PK and IG samples will be separated in aliquots and will be stored frozen until analysis. [redacted] Please see the CPDR001X2101 Laboratory Manual for detailed instructions about collection, handling and shipment of samples. The actual collection date and time of each sample will be entered on the Pharmacokinetics/Immunogenicity [redacted] Blood Collection eCRF pages.

7.2.4 Biomarkers

Biomarker analyses will be used to investigate the effect of the PDR001 at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes. [redacted]

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of Novartis.

The sample collection information must be entered on the appropriate sample collection log eCRF page(s) and requisition form(s). Detailed instructions for the collection, handling, and shipment of tumor samples are outlined in the laboratory manual for the study.

Table 7-8 Biomarker sample collection plan

Sample Type	Visit/ Time point	Volume	Marker	Purpose
Tumor Samples				
Archival tumor sample And newly obtained pre-treatment tumor biopsy	At molecular pre-screening (if needed) or Screening	Archival tumor block or a minimum of 15 newly cut slides from archival paraffin tumor tissue if archival tumor is not available, the newly obtained formalin fixed tumor biopsy in ethanol (3-6 passes) as outlined below will be used.	BRAF V600 (melanoma and anaplastic thyroid cancer), EGFR and/or ALK (NSCLC) [redacted] IHC markers as required (anaplastic thyroid cancer patients only)	Assess molecular status (if molecular status for the indication is unknown and local laboratory test is not feasible) [redacted] Confirm diagnosis of anaplastic thyroid cancer (anaplastic thyroid cancer patients only)

[redacted]

Sample Type	Visit/ Time point	Volume	Marker	Purpose
		Newly obtained formalin fixed tumor biopsy in ethanol (3-6 passes)	[redacted]	Pharmacodynamic (Baseline)

[redacted]

7.2.4.1 Tumor collection

7.2.4.1.1 Potential predictive markers

The status of several immune checkpoint targets and cell populations may be analyzed in archival tumor tissue. [redacted] Other related biomarkers may also be analyzed from this sample, depending on sample availability, resources, and patient's outcomes and as new scientific evidence becomes available.

Submission of an archival tumor sample is requested and will be collected from all patients at screening if not collected at molecular pre-screening. A corresponding pathology report should be included along with the archival sample. If an archival tumor sample is not available, a newly obtained tumor sample is to be obtained and provided as a formalin-fixed biopsy in ethanol. An additional archival sample may be requested if the original sample provided is of insufficient quantity or quality to complete the planned analysis.

7.2.4.1.2 Pharmacodynamic markers

Pharmacodynamic assessments in tumor samples

Newly obtained pre- and on-treatment **paired** tumor samples at Screening/baseline if not collected at molecular pre-screening and between Cycle 3 Day 1 and Cycle 3 Day 15 will be used to assess PDR001 target modulation with established immunohistochemical methods, [redacted]

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

Pharmacodynamic assessments in blood

For pharmacodynamic assessments in blood and plasma, collection of pre- and on-treatment samples as indicated in Table 7-8 will allow the assessment of PD-1 target and pathway modulation in the peripheral blood [redacted] Increases in the number of circulating [redacted], HLA-DR+Ki67+ T cells, IFN-γ, IL-18 and CXCL11 (IFN-γ induced CCK) expressing cells suggests rapid expansion of a pre-existing primed immune response, whilst the decrease of IL-6 is indicative of reduced myeloid-derived suppressor cells (MDSC) (Herbst et al 2014) (Tumeh et al 2014) (Powles et al 2014).

[redacted]

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

After the first primary CSR data cut-off date is reached, no additional samples for pharmacodynamic assessments will be collected.

[redacted]

7.2.4.1.3 Assessment of mechanisms of resistance to PDR001

Mechanisms of resistance to PDR001 will be explored with pretreatment, on-treatment and disease progression tumor samples (archival tumor samples and/or newly collected tumor biopsy samples, as appropriate). Optimal sample collection for the study of resistance will include a newly obtained tumor biopsy taken at screening if not collected at molecular pre-screening, a biopsy taken during therapy (approximately start of cycle 3, alternative times are likely to be acceptable after discussion with Novartis), and a biopsy taken at the time of disease progression / resistance, ideally from a growing lesion if it is safe and feasible for the patient. If a patient has not provided an on therapy tumor sample, they may still be considered for a biopsy at resistance. Duplicate samples will not be collected: specifically, any baseline and on therapy biopsies provided for pharmacodynamic assessments will meet the needs of studying resistance to treatment. The sample at time of disease progression should be collected only from patients who have had a response to treatment as defined by the investigator. This may include a notable period of stable disease and need not require a RECIST or irRC-defined response. The tumor sample at progression of disease should be obtained within 28 days after the last dose of study treatment and no more than 14 days after starting a new antineoplastic therapy. If a patient has progressive disease as best response to treatment, then the biopsy at time of progression of disease should not be collected.

The sample collection information must be entered on the appropriate CRF page(s).

[redacted]

Other assessments

No additional tests will be performed on patients entered into this study.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

For patients with unknown molecular status and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 150 days following the last dose of study treatment. After initiation of new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected in the Adverse Events CRF. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

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

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)

[redacted]

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

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

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

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

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

[redacted]

8.2 Serious adverse events

8.2.1 Definitions

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

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

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

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

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

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

8.2.2 Reporting

For patients with unknown molecular status and who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the

[redacted]

investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular pre-screen failure), SAE collection ends 30 days after the last study related procedure.

For patients who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not. SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 150 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. If a patient starts a post-treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment will be reported to Novartis.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

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

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

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

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

[redacted]

Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. After the mother has provided consent, the newborn will be followed-up for 12 months.

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

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Data Monitoring Committee

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

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of patients will be guided by the BLRM with EWOC, the Bayesian linear model describing the relationship between dose and PDR001 exposure, and a medical review of relevant clinical, PK and laboratory data. Novartis and the investigator parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or recruit an additional cohort of patients at the current dose level (Section 10.4.2 and Section 10.7).

During the phase II part of the study Individual patient data will be reviewed on an ongoing basis and aggregate safety data and the primary endpoint will be monitored quarterly by the

study team across the duration of the trial. The data review and analysis will be based on the available investigator reported data in the clinical database at that time (Section 10.7).

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the

patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

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

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

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

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis.

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements.

Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data summary statistics of mean, standard deviation, median, minimum, and maximum will be presented.

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. Additional data from patients continuing treatment after the data cutoff for the corresponding primary CSR will be reported in a final CSR once all patients have completed study (Section 4.3).

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

- For the 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 will be performed by treatment group.
- For the phase II, all summaries, listings, figures and analyses will be performed by disease group and treatment regimen. Patients from the expansion phase will be classified according to the group to which they were assigned at baseline based on the disease type and regimen. The different groups are:
  - Group 1a: NSCLC, RP2D regimen
  - Group 1b: NSCLC, 300 mg Q3W regimen
  - Group 2: Melanoma, RP2D regimen
  - Group 3: Triple negative breast cancer, RP2D regimen
  - Group 4: Anaplastic thyroid cancer, RP2D regimen

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

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

[redacted]

10.1 Analysis sets

10.1.1 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 (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.

10.1.2 Safety Set

The Safety Set 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:

1. The treatment assigned if it was received at least once, or
2. 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.

10.1.3 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 1.1 as per Appendix 1.
- 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 (see Section 10.4.4). If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

10.1.4 Dose-determining safety set

The DDS consists of all patients from the safety set in the phase I dose escalation part 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 received at least 70% of the planned dose of PDR001 at each time of dosing during Cycle 1.

Patients who do not experience DLT during the first cycle 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.

[redacted]

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 Section 7.1.4.1).

10.1.5 Dose-determining pharmacokinetic 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 $AUC_{(0\text{-}336h)}$.

10.1.6 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 at Phase I.

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.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be listed in detail, and summarized descriptively by treatment group in the phase I part or by Group in the phase II part.

10.3 Treatments (study treatment, concomitant therapies, compliance)

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

These per-patient summaries will, in turn, be summarized using descriptive statistics by treatment group.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by ATC term and treatment group.

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

Compliance with the protocol will be assessed by the number and proportion of patients with protocol deviations. Protocol deviations will be identified prior to database lock and will be listed and summarized.

[redacted]

10.4 Primary objective

Phase I

To estimate the recommended phase 2 dose (RP2D) or the maximum tolerated dose (MTD) for PDR001.

Phase II

To estimate the anti-tumor activity of PDR001.

10.4.1 Variable

Phase I

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

Phase II

The primary variable is the ORR, defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) based on local Investigator assessment, as defined in RECIST 1.1. The true ORR will be estimated upon observed ORR, using a Bayesian analysis.

10.4.2 Statistical hypothesis, model, and method of analysis

Phase I

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 Section 6.2.3.

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.

$$\log(AUC_i) = \log(\alpha) + \beta \log(d_i/d^*) + \varepsilon_i, \qquad \alpha>0,\ \beta>0$$

where $i = 1, \ldots, n$ 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 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:

[redacted]

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

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 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 as detailed in the RAP.

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.

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 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 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; details are described in the RAP.

Phase II

A Bayesian design will be used in order to estimate ORR within each group (Group 1a: NSCLC treated at the RP2D regimen (i.e. Q4W), Group 1b: NSCLC treated at a Q3W regimen, Group 2: melanoma, Group 3: TNBC, Group 4: anaplastic thyroid cancer), 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 Section 5.2). Sample size for each

[redacted]

treatment group is provided in Section 4.1 and details of the sample size calculations in Section 10.8.

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 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 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%.

Group 3 (TNBC): 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, 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.

[redacted]

10.4.3 Handling of missing values/censoring/discontinuations

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

Patients in the phase II part who have Best Overall Response (BOR) of UNK or NA will be considered as a treatment failure in the primary analysis of ORR. Patients with individual scans of UNK or NA will be handled according to RECIST 1.1 as per Appendix 1.

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

10.4.4 Supportive analyses

As a supportive analysis of the primary endpoint for Phase II, a Bayesian hierarchical model with a flexible exchangeability design will be applied on ORR including data from all indications. Exchangeability of indication parameters will be assessed; for the Bayesian methodology and an application to binary data see Thall (2003) and Chugh (2009).

Moreover, the primary analysis of the phase II will be repeated using the PPS.

If there is a substantial number of patients receiving palliative radiotherapy, sensitivity analyses of ORR will be performed where the tumor response assessments are censored at the time of palliative radiotherapy. BOR is determined by the best response recorded between the date of first dose of treatment and date of objectively documented progression or date of subsequent anticancer therapy (including on-treatment palliative radiotherapy of non-target or target lesions), whichever occurs first.

Additional supportive [redacted] analyses will be conducted to support the primary objective, if appropriate, and the details of these analyses will be defined in the RAP.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

Tumor response will be determined per local investigators' assessment. Secondary efficacy endpoints will include BOR, ORR, PFS, DCR and DOR for Phase I and Phase II. In Phase II, BOR and ORR will be defined and analyzed based on tumor assessment by irRC as described in Appendix 14.2 only. PFS, DCR and DOR for Phase II and all secondary efficacy endpoints for Phase I will be defined and analyzed based on tumor assessment by RECIST 1.1 and irRC as described in Appendix 14.1 and Appendix 14.2, respectively.

Definitions for these endpoints according to RECIST 1.1 are provided in Appendix 14.1. Definitions accordingly to irRC are similar to these for RECIST 1.1 and are provided in the RAP.

For irRC the key difference from RECIST in the assessments of these endpoints is the requirement for confirmation of PD not less than 4 weeks after the criteria for PD are first met. The date of the first of these two assessments is then the date of confirmed progression. For

[redacted]

patients who have ended treatment without a valid confirmation assessment, for the purposes of analysis the single assessment of PD will be treated as a confirmed PD. A single assessment of PD followed by a subsequent assessment of SD or better will be considered as a pseudo-progression, and will not be used for analysis.

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. BOR, PFS, DCR and DOR will be listed by patient.

The following analyses will be presented by treatment group for patients treated in the phase II part.

- BOR will be summarized
- ORR (irRC) and DCR will be summarized with an accompanying [90%] exact binomial confidence interval (CI).
- For PFS the survival function will be estimated using the Kaplan-Meier (KM) product limit method and displayed graphically. Median duration, with a two-sided 90% CI, and 25th and 75th percentiles (Brookmeyer 1982, Klein 1997) will be presented. KM estimates of survival proportions at specified time points, along with corresponding 90% CIs (Greenwood's formula, Kalbfleisch 1980) will also be provided.

For DOR, KM estimates may be provided if sufficient numbers of patients respond.

BOR will be listed and summarized, and ORR and DCR will be summarized with an accompanying 90% exact binomial CI by treatment group for all patients treated in the phase I part.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

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 (Section 10.5.3.2).

[redacted]

10.5.3.2 Adverse events (AEs)

Primary summary tables for AEs will include only AEs that started or worsened during the on-treatment period. Additional select summaries will be produced using all related AEs that started or worsened during the combined on-treatment and post-treatment periods.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of AE, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) will be tabulated.

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

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

10.5.3.3 Laboratory abnormalities

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

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

The following by-treatment summaries will be generated separately for hematologyand biochemistry tests:

- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- Listing of all clinically relevant laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

[redacted]

10.5.3.4 Other safety data

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

Definitions of notably abnormal results will be specified in the RAP.

- shift table baseline to worst on-treatment result

[redacted]

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

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

10.5.4 Pharmacokinetics

The pharmacokinetic parameters that will be assessed are presented in Table 10-1.

Table 10-1 Noncompartmental pharmacokinetic parameters

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

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

Pharmacokinetic variables:

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

- AUCinf, AUC0-336h, Cmax, Tmax, T1/2, CL and Vz.

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

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

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

[redacted]

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.

[redacted]

Dose proportionality

The analysis of dose proportionality will be conducted for AUC and Cmax 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.

Immunogenicity –exposure and/or adverse event relationship

The concentration/adverse event – immunogenicity relationship will be explored graphically, tabulated and, if appropriate, characterize a relationship between the changes from screening immunogenicity presence and serum concentration of PDR001.

In addition, the potential correlation between immunogenicity and other endpoints (major safety, efficacy, [redacted] biomarker parameters) may be evaluated.

[redacted]

[redacted]

10.7 Interim analysis

No formal interim analyses are planned.

However, in phase I, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose escalation part, the next dose will be chosen depending on the observed data (based on safety, tolerability, PK, PD and efficacy data, guided by the recommendations from the BLRM of DLT using EWOC, the Bayesian linear model of dose-exposure relationship and recommendations from participating investigators). Details of this procedure and the process for communication with Investigators are provided in Section 6.2.3.

Data from patients in the phase II part will be reviewed on an ongoing basis to monitor the safety and tolerability of the RP2D in that part of the study.

10.8 Sample size calculation

Phase I

Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation part including at least six patients at the RP2D/MTD level, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts may be opened to enroll patients at any previously tested dose level on or below the estimated RP2D/MTD for further elaboration of safety and pharmacokinetic parameters as required. At least 21 patients are expected to be treated in the dose escalation part, for the model to have reasonable operating characteristics relating to its MTD recommendation. RP2D recommendation may be made with fewer patients.

Phase II

Nivolumab achieved an ORR of 19% in patients with NSCLC based on the Phase III CheckMate057 trial with 292 patients treated with Nivolumab (Paz-Ares 2015). Therefore an ORR of 20% will be used as the reference ORR for patients with NSCLC treated with PDR001 in the Phase II part of the study.

Nivolumab achieved an ORR of 32% in patients with melanoma based on the Phase III CheckMate037 trial with 120 patients treated with Nivolumab (Weber 2015). Therefore an ORR of 30% will be used as the reference ORR for patients with melanoma treated with PDR001 in the Phase II part of the study.

There is limited published ORR data for patients with TNBC treated with nivolumab or pembrolizumab. Pembrolizumab achieved an ORR of 18.5% in patients with TNBC based on a small study (n= 32 patients treated with pembrolizumab (Nanda 2014). Therefore, an ORR of 20% will be used as the reference ORR for patients with TNBC treated with PDR001 in the Phase II part of the study.

There are no published response data identified at time of this protocol development for anaplastic thyroid cancer patients treated with nivolumab or pembrolizumab.

Approximately 60 patients per disease group will be enrolled to Groups 1a, 1b and 2, which include the two “benchmark diseases” NSCLC and melanoma. Approximately 40 patients will be enrolled to Group 3 (TNBC). Approximately 10 patients will be enrolled to Group 4 (anaplastic thyroid cancer). The relatively small size of the anaplastic thyroid cancer group reflects the low prevalence of this disease; this group may be increased in size to approximately 40 patients based on feasibility of enrollment and if PDR001 appears to be active in this disease. Further details on the patient population are provided in Section 5.2.

It is assumed that efficacy will be claimed if observing an ORR of ≥ 20% (NSCLC), ≥ 30% (melanoma) and ≥ 20% (TNBC).The operating characteristics of the design are provided in Table 10-2. Specifically:

- If the true ORR is 10% for NSCLC (group 1a or 1b) (i.e. in the unacceptable efficacy range), the probability of observing an ORR ≥ 20% is 1.5% (<5%).
- If the true ORR is 15% for melanoma (i.e. in the unacceptable efficacy range), the probability of observing an ORR ≥ 30% is 0.2% (< 5%).

[redacted]

- If the true ORR is 10% for TNBC (i.e. in the unacceptable efficacy range), the probability of observing an ORR ≥ 20% is 4.2% (< 5%).
- If the true ORR is 30% for NSCLC (group 1a or 1b) (i.e. in the clinically significant efficacy range), the probability of observing an ORR ≥ 20% is 97.1%.
- If the true ORR is 40% for melanoma (i.e. in the clinically significant efficacy range), the probability of observing an ORR ≥ 30% is 95.9%.
- If the true ORR is 30% for TNBC (i.e. in the clinically significant efficacy range), the probability of observing an ORR ≥ 20% is 94.5%.

Table 10-2 Operating characteristics of the design (probability to declare efficacy)

	Groups 1a and 1b: NSCLC, n=60 per group	Group 2: Melanoma, n=60	Group 3: TNBC, n=40
True ORR	**Probability to observe an ORR ≥ 20%**	**Probability to observe an ORR ≥ 30%**	**Probability to observe an ORR ≥ 20%**
10%	1.5%	0.0%	4.2%
15%	18.1%	0.2%	24.4%
20%	55.1%	4.3%	56.3%
25%	85.2%	22.5%	81.8%
30%	97.1%	54.9%	94.5%
40%	100.0%	95.9%	99.8%

Table 10-3 summarizes the 90% Credible Interval for the true ORR at each of the observed ORR for the four disease groups. The table shows that with observed ORR of 20% at the planned sample size for Group 1a/b, 30% for Group 2, 20% for Group 3, and 20% for Group 4, the lower bound of 90% CI is greater than 10% (the threshold of unacceptable efficacy for NSCLC and TNBC), 15% (the threshold of unacceptable efficacy for melanoma) and is around 5%/11% for anaplastic thyroid cancer (n=10/40) accordingly.

Table 10-3 Observed ORR and 90% Credible Interval

	Groups 1a and 1b: NSCLC, n=60 per group	Group 2: Melanoma, n=60	Group 3: TNBC, n=40	Group 4: Anaplastic thyroid cancer, n=10	Group 4: Anaplastic thyroid cancer, n=40
Observed ORR	20%	30%	20%	10% / 20%	10% / 20%
90% CI of ORR	[12.2%, 28.9%]	[20.6%, 39.7%]	[10.8%, 30.9%]	[1.0%, 29%] / [4.7%, 41.5%]	[3.8%, 19%] / [10.8%, 30.9%]

10.9 Power for analysis of key secondary variables

Not applicable

[redacted]

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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

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

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

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11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

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

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

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

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

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

11.6 Study documentation, record keeping and retention of documents

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

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Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

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12 Protocol adherence

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

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

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

Harmonization of Efficacy Analysis of Solid Tumor Studies

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
[redacted]	[redacted]
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

[redacted]

14.1.1 Introduction

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

The efficacy assessments described in Section 14.1.2 and the definition of best response in Section 14.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.1.4 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.1.2 Efficacy assessments

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

14.1.2.1 Definitions

14.1.2.1.1 Disease measurability

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

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

For patients without measurable disease see Section 14.1.3.2.8.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

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- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.1.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.1.3.2.8.

14.1.2.2 Methods of tumor measurement - general guidelines

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

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

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

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- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions

[redacted]

and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

- **Clinical examination:** Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.1.2.3 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.1.2.1.1.
- **Nodal target:** See Section 14.1.2.1.1.

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

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

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately

[redacted]

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

14.1.2.4.1 Follow-up and recording of lesions

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

Non-nodal lesions

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

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

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

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

Nodal lesions

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

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

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

[redacted]

14.1.2.4.2 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm.[1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.[2]
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
3. Methodology change See Section 14.1.2.2.

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However,

[redacted]

in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

[redacted]

14.1.2.4.3 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

1. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion

[redacted]

- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.1.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.2.2.

14.1.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-3.

Table 14-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. This overall lesion response also applies when there are no non-target lesions identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 14.1.2.4.

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

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.1.3 Efficacy definitions

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

[redacted]

14.1.3.1 Best overall response

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

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 150 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

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

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a

PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

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

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

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

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

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

The primary analysis of the best overall response will be based on the sequence of investigator overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

[redacted]

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

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

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

14.1.3.2 Time to event variables

14.1.3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

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

[redacted]

14.1.3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If

[redacted]

a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.1.3.2.4 Time to treatment failure

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

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

14.1.3.2.5 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

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

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

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

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

[redacted]

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

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

14.1.3.2.6 Time to response

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

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

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

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

[redacted]

Start dates

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

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

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.3.2.8).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

14.1.3.2.8 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

[redacted]

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-4.

Table 14-4 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 14.1.2.4.

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

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

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

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

14.1.3.2.9 Sensitivity analyses

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

Based on definitions outlined in Section 14.1.3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics-April 2005) as a reference, the following analyses can be considered:

[redacted]

Table 14-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)
[1] =Definitions can be found in Section 14.1.3.2.7.			
[2] =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.3.2.7.			
[3] =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.			

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead

[redacted]

of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

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

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

14.1.4 Data handling and programming rules

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

14.1.4.1 Study/project specific decisions

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

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

14.1.4.2 End of treatment phase completion

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

The end of treatment visit and its associated assessments should occur within 14 days of the last study treatment.

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

- Adverse event(s)

[redacted]

- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Subject/guardian decision
- Death
- Progressive disease per irRC (not per RECIST)
- Study terminated by the sponsor

14.1.4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

14.1.4.4 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

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

[redacted]

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

14.1.4.5 Programming rules

The following should be used for programming of efficacy results:

14.1.4.5.1 Calculation of 'time to event' variables

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

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

14.1.4.5.2 Incomplete assessment dates

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

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.1.3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

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

14.1.4.5.3 Incomplete dates for last known date patient alive or death

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

14.1.4.5.4 Non-target lesion response

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

14.1.4.5.5 Study/project specific programming

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

14.1.4.5.6 Censoring reason

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

For survival the following censoring reasons are possible:

[redacted]

- Alive
- Lost to follow-up

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (option
- Death due al, see Table 14-5) to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.1.3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

14.1.5 References (available upon request)

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

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

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465.

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18.

[redacted]

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16.

[redacted]

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

14.2.1 Introduction

The purpose of this document is to summarize the immune-related Response Criteria (irRC) (Wolchol et al 2009) using one-dimensional measurements (Nishino et al 2013) that will be used to assess tumor response.

The definition of target/non target lesions, the criteria for lesion measurement, number of lesions that can be assessed and method of evaluation are the same for irRC and RECIST 1.1 and are available in the RECIST 1.1 guidelines (Appendix 1).

This appendix outlines the specificities for irRC evaluation.

14.2.2 New lesions and non-target lesions

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

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

New measureable lesions are defined using the same criteria as for baseline target lesions in RECIST 1.1. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measurable lesions. Up to five new measurable lesions (and a maximum of two per organ) are allowed in total and will be included in the overall tumor assessment.

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

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

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

[redacted]

14.2.4 Definitions of response categories and evaluation of overall lesion response

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

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

The response categories are defined as follows:

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

[redacted]

Table 14-6 Overall response at each assessment

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

*the diameter of new measurable lesions is included in the calculation of the sum of diameters.
[a] to be confirmed after at least 4 weeks.
[b] from baseline
[c] from nadir

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

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the irCR.

14.2.5 Only non-measurable disease at baseline

For patients with only non-measurable disease at baseline, unequivocal progression of non-target lesions will constitute an irPD (i.e. worsening of the overall tumor burden which is substantial enough to lead to discontinuation or change of therapy). In addition, the appearance of new lesions (measurable or non-measurable) consistent with unequivocal progression taking into account the overall disease burden will constitute an irPD. The absence of all non-target lesions and no new lesions will qualify for irCR. Otherwise the overall response will be considered as irNon-CR/Non-PD (irNCRNPD) similar to RECIST 1.1. Confirmation of irPD and irCR is required, as specified above in Section 14.2.4. If any baseline non-target lesion or a new lesion observed at an earlier post-baseline evaluation was not/could not be assessed at a later post-baseline tumor evaluation, then the overall response will be irUNK. No confirmation is required for irNCRNPD.

14.2.6 References (available upon request)

Bohnsack O, Ludajic K, Hoos A (2014) Adaptation of the immune-related response criteria: irRECIST. ESMO 2014; Abstract 4958 visible at: https://www.webges.com/cslide/library/esmo/browse/search/eTT#9faE02tu.

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

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

[redacted]

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

The dose recommendations and estimation of the RP2D/MTD during the escalation part of the study will be guided by both PDR001 exposure and the DLT rate. The dose-exposure relationship will be estimated for PDR001 via a Bayesian linear regression 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. Dose recommendation based on DLT rate will be guided by the escalation with overdose control (EWOC) principle. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by Rogatko (2007) and is one of the key elements of the FDA's Critical Path Initiative.

14.3.1 Bayesian linear regression model

14.3.1.1 Introduction

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

$$\log(AUC_i) = \log(\alpha) + \beta \log(d_i/d^*) + \varepsilon_i, \qquad \alpha>0, \beta>0 \qquad (1)$$

where $i = 1, \ldots, n$ is the i-th subject in the study, d_i is the dose received by the i-th subject, AUC_i is the area under curve of PDR001 concentrations for the i-th subject during the interval of 0 to 336 hours 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. As a consequence $\log(\alpha)$ is equal to the predicted mean of log(AUC) at d*. Since a Bayesian approach is used, prior distributions need to be specified for parameters $\log(\alpha)$, $\log(\beta)$, and σ.

14.3.1.2 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).

MAP priors assume similarity (exchangeability) of model parameters among trials for the three molecules: Nivolumab, Pembrolizumab and PDR001. Assuming $\log(\alpha_h)$, $\log(\beta_h)$ and σ_h are the parameters for the h^{th} previous study, a MAP prior distribution for the parameters in the new study is given by the predictive distribution of $\log(\alpha^*)$, $\log(\beta^*)$, and σ^* in the following model:

$$(\log(\alpha_h), \log(\beta_h)) \sim \text{BVNormal}((\mu_a, \mu_b), \Psi),\ \sigma_h \sim LN(\mu_s, \tau_s^2),\ h = 1, 2, 3$$

$$(\log(\alpha^*), \log(\beta^*)) \sim \text{BVNormal}((\mu_a, \mu_b), \Psi),\ \sigma^* \sim LN(\mu_s, \tau_s^2)$$

where Ψ is the between-trial variance-covariance matrix for $(\log(\alpha), \log(\beta))$, with standard deviations τ_a, τ_b and correlation coefficient ρ. BVNormal refers to the bivariate normal distribution; LN refers to the log-normal distribution.

1. The priors for hyper-parameters in the model were set as follows:

[redacted]

Table 14-7 Prior distributions of model hyper-parameters (N=Normal, LN= Log-Normal)

Parameter	Prior	Median (95% interval)
μ_a	N(6, 10^2)	"flat"
τ_a	LN(-0.693, 0.707^2)	0.5 (0.125, 2)
μ_b	N(0, 0.354^2)	0 (-0.693, 0.693)
τ_b	LN(-2.079, 0.354^2)	0.125 (0.063, 0.25)
ρ	Uniform(-1, 1)	
μ_s	N(-1.386, 0.707^2)	-1.386 (-2.772, 0)
τ_s	LN(-1.386, 0.707^2)	0.25 (0.063, 1)

The parameters τ_a, τ_b and τ_s quantify the degree of between trial heterogeneity on the intercept, log(slope) and error standard deviation of the dose-exposure regression model, respectively. The choices of prior for those parameters reflect the assumption that the exposure at d^* may vary considerably between the different compounds but the slope may be similar.

2. Published summary data on Nivolumab and Pembrolizumab from three studies are available (see Section 14.3.1.3) and summarized in Table 14-8 after unit conversion is applied on source data.

Table 14-8 Geometric mean (micro gram day/mL) and geometric CV% of AUC data from three Nivolumab or Pembrolizumab studies

Dose (mg/kg)	Study 1		Study 2		Study 3	
	N	G. Mean (CV%)	N	G. Mean (CV%)	N	G. Mean (CV%)
1	3	160 (20)			37	92 (34)
2			89	643 (37)		
3	3	975 (24)			42	323 (46.5)
10	8	2282 (31)	83	2770 (33)	52	1526 (59)

The geometric mean and CV% of AUC data can be converted to the sample mean (SM) and sample variance (SV) of log(AUC) through the equations:

SM in log scale = log(geometric mean)

SV in log scale = $\log(1+(CV\%/100)^2)$

The distributions of aggregate data were then used to capture the data likelihood as follows:

$SM_{h,d} \sim N((\log(\alpha_h) + \beta_h \log(d/d^*)), \sigma_h^2/n_{h,d})$

$SV_{h,d} \sim \text{Gamma}((n_{h,d}-1)/2, (n_{h,d}-1)/(2\sigma_h^2))$

where $n_{h,d}$, $SM_{h,d}$ and $SV_{h,d}$ are the sample size, sample mean and sample variance of log(AUC) for the dose group d and trial h, respectively.

3. The MAP distributions were derived based on the priors in step 1 and available previous study result summary in step 2. A Normal distribution was used to approximate the MAP distribution for log(σ). For the regression coefficients (log(α), log(β)), 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

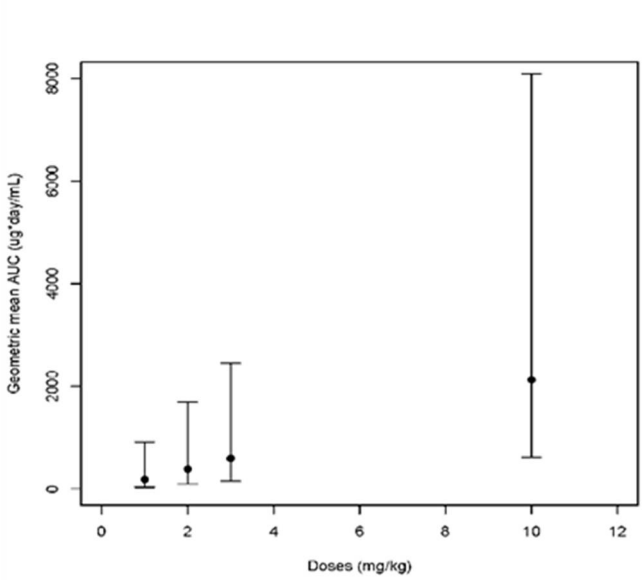
component. The respective distribution for each component and its weight is provided in Table 14-9.

Table 14-9 Prior distribution of (log(Alpha), log(Beta)) and sigma for the new trial

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

Figure 14-1 shows a visualization of the geometric mean AUC at each interested dose level together with a 95% interval, predicted by the priors in Table 14-9.

Figure 14-1 Visualization of the mean AUC



14.3.1.3 AUC data on Nivolumab and Pembrolizumab

Study 1 (Pembrolizumab, Patnaik et al 2012)

Table 14-10 Area under the pembrolizumab concentration versus time curve by treatment arm

Dose (mg/kg)	N	$AUC_{0\text{-}28day}$ (CV %)*
1	3	160 (20)
3	3	975 (24)
10	8	2282 (31)

* Numbers presented are assumed to be geometric mean in μg·day/mL and geometric CV %.
Profile supports dosing every 2 or 3 weeks.

[redacted]

Study 2 (Pembrolizumab, Robert et al 2014)

Table 14-11 Area under the pembrolizumab concentration versus time curve at steady state by treatment arm

	2 mg/kg Q3W n=89	10 mg/kg Q3W n=83
Median, g•day/L	0.654	3.76
Geometric mean, g•day/L	0.643	3.77
Geometric CV, %	37	33
5th and 95th percentiles, g•day/L	0.345–1.12	2.13–5.99
Range, g•day/L	0.254–1.27	1.85–7.00

Study 3 (Nivolumab, Brahmer et al 2012)

"Serum levels of anti–PD-L1 antibody increased in a dose-dependent manner from 1 to 10 mg per kilogram in 131 patients who were evaluated. The geometric mean area under the curve (0 to 14 days) for doses of 1 mg, 3 mg, and 10 mg per kilogram were 2210, 7750, and 36,620 µg per milliliter per hour, respectively (coefficient of variation, 34 to 59%)."

This information is summarized in Table 14-12:

Table 14-12 Area under the nivolumab concentration versus time curve by dose level

Dose (mg/kg)	N*	$AUC_{0\text{-}14day}$ Geometric Mean (µg•hour/mL)	$AUC_{0\text{-}14day}$ Geometric CV %
1	37	2210	34
3	42	7750	46.5**
10	52	36,620	59

* Numbers of treated patients are 37, 42, and 125 for 1 mg, 3 mg, and 10 mg per kilogram, respectively. Total number of patients evaluated in this summary is 131 across three dose groups. Assuming only part of the 125 patients in the 10 mg/kg dose group had AUC assessments, the distribution of the 131 patients are assumed to be 37, 42, and 52 for 1 mg, 3 mg, and 10 mg per kg.
** The CV% for 3 mg/kg is assumed to be the average of CV % of 1 mg/kg and 10 mg/kg.

14.3.1.4 Operating characteristics of Bayesian dose-exposure design

Scenarios of dose-exposure relationship

In order to show how the BLM design performs, 5 hypothetical profiles of dose-exposure relationship were investigated using simulations:

- Profile 1: exposure increases with dose following the same trend as Nivolumab and Pembrolizumab; 3 mg/kg and higher doses meet the target exposure
- Profile 2: exposure increases with dose following the same trend as Nivolumab and Pembrolizumab; only 10 mg/kg meets the target exposure
- Profile 3: exposure increases with dose following the same trend as Nivolumab and Pembrolizumab; all doses at 1 mg/kg and higher meet the target exposure
- Profile 4: exposure increases slowly with dose increasing; 3 mg/kg and higher doses meet the target exposure

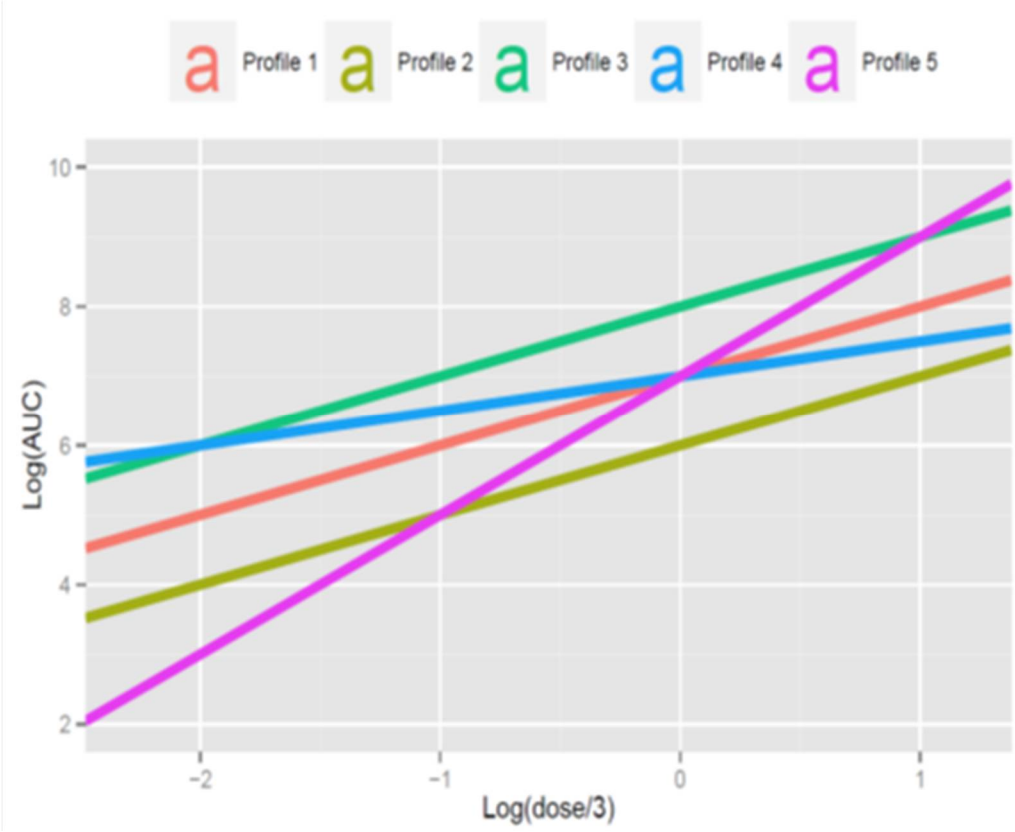
[redacted]

- Profile 5: exposure increases rapidly with dose increasing; 3 mg/kg and higher doses meet the target exposure

Table 14-13 Hypothetical profiles of dose-exposure relationship used in simulations

			AUC (µg•day/mL)		
Profile	**BLM intercept - log(alpha)**	**BLM slope - beta**	**1 mg/kg**	**3 mg/kg**	**10 mg/kg**
1	7	1	366	**1097**	3655
2	6	1	134	403	**1345**
3	8	1	**994**	2981	9937
4	7	0.5	633	**1097**	2002
5	7	2	122	**1097**	12185

Figure 14-2 Visualization of five hypothetical profiles



Simulation parameters

To examine the data sufficiency, four sample set with various sample sizes ranging from 18 to 24 were considered for each dose-exposure profile:

1. 6 patients at each dose level (1 mg/kg, 3mg/kg, and 10 mg/kg); total N = 18
2. 3, 9, 6 patients at 1 mg/kg, 3mg/kg, and 10 mg/kg, respectively; total N = 18
3. 3, 12, 6 patients at 1 mg/kg, 3mg/kg, and 10 mg/kg, respectively; total N = 21
4. 3, 12, 9 patients at 1 mg/kg, 3mg/kg, and 10 mg/kg, respectively; total N = 24

There are total 20 scenarios to be simulated combining 5 dose-exposure profiles and 4 sample set considerations. 500 trials were used to simulate each of the 20 scenarios. For each trial, the AUC data for individual patients were randomly generated from a Log-Normal distribution where

log(AUC) ~ Normal(log(mean as specified in Table 14-13), standard deviation =0.4).

For each simulated trial, the Bayesian Linear Regression Model was implemented using the simulated AUC data with the priors specified in Section 14.3.1.2.

Metrics

There are a set of operating characteristics and metrics evaluated based on the simulations to compare the relative performance under each true scenario. The metrics reviewed include:

1. Average posterior mean exposure at 1 mg/kg, 3mg/kg, and 10 mg/kg
2. Average posterior probability of exposure greater than 1000 µg•day/mL at 1 mg/kg, 3mg/kg, and 10 mg/kg
3. Average posterior probability of exposure lying in the interval of 800 - 1200 µg•day/mL at 1 mg/kg, 3mg/kg, and 10 mg/kg
4. Percentage of trials where the posterior mean exposure is at least 1000 µg•day/mL at 1 mg/kg, 3mg/kg, and 10 mg/kg
5. Percentage of trials where the posterior probability of exposure greater than 1000 µg•day/mL is at least 50% at 1 mg/kg, 3mg/kg, and 10 mg/kg
6. Percentage of trials where the posterior probability of exposure lying in the interval of 800 - 1200 µg•day/mL at 1 mg/kg is the highest among 3 doses; similar percentage will be calculated for 3 mg/kg and 10 mg/kg

The evaluation indicated that the model is performing appropriately under the 20 scenarios.

Results

Table 14-14 summarizes the probabilities of the dose recommended from the model for the five different profiles and four sample sets studied. Based on the dose-exposure analysis, a dose is recommended for a trial if this dose meets the following criteria:

(1) posterior mean exposure at this dose ≥ 1000 µg•day/mL, and

(2) posterior probability of exposure greater than 1000 µg•day/mL > 50%.

[redacted]

Table 14-14 Summary of recommendation rate for all profiles and sample sets at various doses based on the dose recommendation criteria (1) and (2)

		Probability (%) that a dose level is recommended							
Profile	Sample Set	0.3 mg/kg	1 mg/kg	2 mg/kg	3 mg/kg	5 mg/kg	7 mg/kg	9 mg/kg	10 mg/kg
1	1	0	0	0	76	100	100	100	100
	2	0	0	0	77	100	100	100	100
	3	0	0	0	79	100	100	100	100
	4	0	0	0	82	100	100	100	100
2	1	0	0	0	0	0	49	99	100
	2	0	0	0	0	0	48	99	100
	3	0	0	0	0	0	48	99	100
	4	0	0	0	0	0	42	99	100
3	1	0	47	100	100	100	100	100	100
	2	0	50	100	100	100	100	100	100
	3	0	51	100	100	100	100	100	100
	4	0	52	100	100	100	100	100	100
4	1	0	0	3	83	100	100	100	100
	2	0	0	1	63	100	100	100	100
	3	0	0	0	70	100	100	100	100
	4	0	0	0	61	100	100	100	100
5	1	0	0	0	81	100	100	100	100
	2	0	0	0	84	100	100	100	100
	3	0	0	0	86	100	100	100	100
	4	0	0	0	87	100	100	100	100

Table 14-15 below summarizes the percentages of the recommended dose of the model for the five different profiles and four sample set studied. Based on the dose-exposure analysis, a dose is recommended for a trial if this dose meets the criteria (1) and (2) and the following added criteria (3):

(3) Highest posterior probability of exposure lying in the interval of 800 - 1200 µg•day/mL among all provisional doses (e.g. 0.3, 1, 2, 3, 5, 7, 9 and 10 mg/kg).

[redacted]

Table 14-15 Summary of recommendation rate for all profiles and samples set at various doses based on the dose recommendation criteria (1), (2), and (3)

		Probability (%) that a dose is recommended				
Profile	Sample Set	1 mg/kg	3 mg/kg	10mg/kg	Other doses recommended	No dose recommended
1	1	0	65	0	0	35
	2	0	64	0	0	36
	3	0	68	0	0	32
	4	0	71	0	0	29
2	1	0	0	0	51	49
	2	0	0	0	53	47
	3	0	0	0	50	50
	4	0	0	0	50	50
3	1	47	0	0	0	53
	2	49	0	0	0	50
	3	51	0	0	0	49
	4	52	0	0	0	48
4	1	0	54	0	3	44
	2	0	49	0	1	50
	3	0	56	0	1	43
	4	0	51	0	0	49
5	1	0	81	0	0	19
	2	0	83	0	0	17
	3	0	86	0	0	14
	4	0	87	0	0	13

The simulated operating characteristics presented show that the Bayesian Linear Model performs well under the hypothetical profiles investigated. In conclusion, the simulations performed illustrate that the model has reasonable operating characteristics.

14.3.2 Bayesian logistic regression model (BLRM)

14.3.2.1 Introduction

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

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

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.

[redacted]

14.3.2.2 Prior specifications

Prior for (log(α), log(β)):

This study uses a mixture prior consisting of two components. Component 1 is the distribution derived based on PDR001 preclinical data and data on Nivolumab and Pembrolizumab, and is also the component to allow for a less dose toxicity case. The assigned weight for component 1 is 80%. Component 2 allows for a more dose toxicity case. The assigned weight for mixture for component 2 is 20%.

Component 1:

A weakly informative bivariate normal prior for the model parameters (log(α), log(β)) is assumed based on prior information (medians) for the probabilities of DLT at each dose, from PDR001 preclinical data and data on Nivolumab and Pembrolizumab, and considering wide confidence intervals. The priors are obtained as follows:

- For the purposes of tuning the prior for the BLRM model, the median DLT rate at 1 mg/kg Q2W is assumed to be at 5%, and the median DLT rate at 10 mg/kg Q2W is assumed to be at 10%. For the remaining doses, median DLT rates a priori are assumed linear in the logit-scale as a function of log-dose.
- Based on the above specified medians for the DLT rate at certain dose and wide prior confidence intervals, the optimal parameters of the bivariate normal distribution can be obtained following the procedure described by (Neuenschwander et al 2008). Based on Neuenschwander's procedure, the initial set of prior (-2.692, -1.26, 2.484, 0.745, -0.765) is derived.
- The initial set of prior is then fine-tuned in combination with the component 2 prior, by adjusting the SD of log(α) and log(β) as well as setting the correlation between log(α) and log(β) = 0, to achieve reasonable performance for the hypothetical dose-escalation scenarios in Section 14.3.2.3.
- The Component 1 is set to be (-2.692, -1.26, 1.0, 1.0, 0)

Component 2:

- This high-toxicity component is a vague bivariate normal prior derived by assuming median probabilities of DLT at 1, 3, 10 mg/kg are 3%, 9%, 25%, respectively, as well as a log-linear relationship between dose strength and the odds of DLT as defined in Section 14.3.2.1. By fixing the log(β) at 0, the log(α) value is adjusted to achieve estimated probability of DLT (using the equation $\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*)$) at 1, 3, 10 mg/kg being 3%, 9%, 25% respectively, which results in log(α) being -2.3. At the meanwhile, setting SD of log(α) = 2 and log(β) = 1, and setting the correlation between log(α) and log(β) = 0 to complete the determination of the component 2.
- The component 2 is set to be (-2.3, 0, 2, 1, 0)

All the information to derive the prior distributions for the model parameters is provided in Table 14-16.

[redacted]

Table 14-16 Prior distribution of model parameters

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

Table 14-17, Table 14-18 and Table 14-19 summarize the DLT rates of the associated prior distribution. The doses not meeting the overdose criteria are bold in the table, i.e. it is not eligible at the start of the study (under the prior).

Table 14-17 Summary of prior distribution of DLT rates (derived from the mixture prior in Table 14-16)

(Table 14-16)

PDR001 dose (mg/kg Q2W)	Prior probabilities that Pr(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16,0.33)	[0.33, 1]	Mean	SD	2.50%	50.00%	97.50%
0.3	0.939	0.047	0.014	0.049	0.076	0	0.024	0.252
1 (starting dose)	0.9	0.075	0.026	0.069	0.095	0.001	0.039	0.334
3	0.805	0.134	0.061	0.11	0.133	0.006	0.066	0.518
10	0.615	0.2	0.185	0.205	0.233	0.012	0.114	0.946

Note: bold values indicate doses not meeting the overdose criterion (more than 25% chance of excessive toxicity) with the prior information only.

Table 14-18 Summary of prior distribution of DLT rates (derived from the Component 1 prior in Table 14-16)

(Table 14-16)

PDR001 dose (mg/kg Q2W)	Prior probabilities that Pr(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16,0.33)	[0.33, 1]	Mean	SD	2.50%	50.00%	97.50%
0.3	0.948	0.046	0.006	0.048	0.059	0	0.028	0.216
1 (starting dose)	0.918	0.071	0.011	0.064	0.069	0.004	0.041	0.257
3	0.849	0.127	0.024	0.09	0.084	0.009	0.064	0.327
10	0.683	0.211	0.106	0.151	0.154	0.013	0.1	0.603

Note: bold values indicate doses not meeting the overdose criterion (less than 25% chance of excessive toxicity) with the prior information only.

[redacted]

Table 14-19 Summary of prior distribution of DLT rates (derived from the Component 2 prior in Table 14-16)

(Table 14-16)

PDR001 dose (mg/kg Q2W)	Prior probabilities that Pr(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16,0.33)	[0.33, 1]	Mean	SD	2.50%	50.00%	97.50%
0.3	0.898	0.053	0.048	0.056	0.129	0	0.006	0.496
1 (starting dose)	0.821	0.09	0.089	0.095	0.167	0	0.022	0.653
3	0.624	0.162	0.214	0.193	0.231	0.002	0.092	0.838
10	0.345	0.154	**0.501**	0.42	0.346	0.006	0.332	0.999

Note: bold values indicate doses not meeting the overdose criterion (less than 25% chance of excessive toxicity) with the prior information only.

To check the performance of the model, the document summarizes some hypothetical dose escalation scenarios. Details regarding dose recommendation are described in Section 10.4.2 of the protocol.

14.3.2.3 Hypothetical dose escalation scenarios based on DLT data alone

In order to show how the Bayesian model performs, different hypothetical dose escalation scenarios were investigated. The design should make reasonable dose-recommendations during the clinical trial based on the observed DLTs for hypothetical dose escalation scenarios. During the study, the decision to dose escalate after completion of a given cohort and the actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM per EWOC principle, estimated/predicted exposure at each dose level, and medical review of available clinical and laboratory data.

Some hypothetical dose escalation scenarios to illustrate the dose escalation up to the fourth dose cohort are listed in Table 14-20. The maximum dose increment allowed in the scenarios did not exceed 334% as per escalation rules defined in Section 6.2.3. The recommended next dose level satisfied the EWOC principle.

Table 14-20 Hypothetical dose escalation scenarios for on-study decisions

Scenario	Cohort	PDR001 Dose level (mg/kg)	N pat	N tox	Next Dose Level (NDL)	P(Target) NDL	P(Over) NDL	Median DLT rate (NDL)
1	1A	1	4	0	3	0.104	0.025	0.054
2	1A	1	4	1	3	0.26	0.114	0.121
3	1A	1	4	2	1	0.37	0.21	0.186
4	1A 2A	1 3	4 3	0 0	10	0.156	0.106	0.079
5	1A 2A	1 3	4 3	0 1	3	0.2	0.055	0.097

[redacted]

Scenario	Cohort	PDR001 Dose level (mg/kg)	N pat	N tox	Next Dose Level (NDL)	P(Target) NDL	P(Over) NDL	Median DLT rate (NDL)
6	1A	1	4	0				
	2A	3	3	2				
					1	0.201	0.031	0.087
7	1A	1	4	0				
	2A	3	3	0				
	3A	3	3	0				
					10	0.122	0.094	0.07
8	1A	1	4	0				
	2A	3	3	0				
	3A	3	3	1				
					10	0.243	0.187	0.138
9	1A	1	4	0				
	2A	3	3	0				
	3A	3	3	2				
					3	0.334	0.084	0.141
10	1A	1	4	0				
	2A	3	3	1				
	3A	3	3	0				
					10	0.243	0.187	0.138
11	1A	1	4	0				
	2A	3	3	1				
	3A	3	3	1				
					3	0.334	0.084	0.141
12	1A	1	4	0				
	2A	3	3	1				
	3A	3	3	2				
					1	0.233	0.034	0.1
13	1A	1	4	0				
	2A	3	3	2				
	3A	1	3	0				
					3	0.321	0.241	0.181
14	1A	1	4	0				
	2A	3	3	2				
	3A	1	3	1				
					1	0.352	0.07	0.142
15	1A	1	4	0				
	2A	3	3	2				
	3A	1	3	2				
					1	0.505	0.208	0.222
16	1A	1	4	1				
	2A	1	3	0				
					3	0.217	0.065	0.103

[redacted]

Scenario	Cohort	PDR001 Dose level (mg/kg)	N pat	N tox	Next Dose Level (NDL)	P(Target) NDL	P(Over) NDL	Median DLT rate (NDL)
17	1A	1	4	1				
	2A	1	3	1				
					3	0.384	0.171	0.175
18	1A	1	4	1				
	2A	1	3	2				
					1	0.456	0.247	0.225
19	1A	1	4	1				
	2A	1	3	0				
	3A	3	3	0				
					10	0.243	0.099	0.117
20	1A	1	4	1				
	2A	1	3	0				
	3A	3	3	1				
					10	0.373	0.248	0.198
21	1A	1	4	1				
	2A	1	3	0				
	3A	3	3	2				
					1	0.352	0.07	0.142
22	1A	1	4	1				
	2A	1	3	0				
	3A	3	3	0				
	4A	3	3	0				
					10	0.2	0.061	0.1
23	1A	1	4	1				
	2A	1	3	0				
	3A	3	3	0				
	4A	3	3	1				
					10	0.367	0.164	0.168
24	1A	1	4	1				
	2A	3	3	1				
	2B	1	3	0				
	3A	3	5	1				
					3	0.423	0.06	0.155
25	1A	1	4	0				
	2A	3	5	1				
	2B	1	3	0				
					10	0.232	0.208	0.138
26	1A	1	4	0				
	2A	3	5	1				
	2B	1	3	0				
	3A	10	6	1				
	3B	3	4	0				
					30	0.322	0.223	0.175

[redacted]

Scenario	Cohort	PDR001 Dose level (mg/kg)	N pat	N tox	Next Dose Level (NDL)	P(Target) NDL	P(Over) NDL	Median DLT rate (NDL)
27	1A	1	3	0				
	2A	3	4	0				
	2B	1	3	0				
					10	0.124	0.107	0.073
28	1A	1	3	0				
	2A	3	4	0				
	2B	1	3	0				
	3A	10	6	1				
	3B	3	6	1				
					30	0.32	0.212	0.171
29	1A	1	3	0				
	2A	3	5	2				
	3A	1	3	1				
					3	0.461	0.178	0.198
30	1A	1	3	0				
	2A	3	5	2				
	3A	1	3	1				
	4A	1	4	0				
					3	0.427	0.125	0.173

Cohort naming convention: the number identifies the cohort number, the letter “A” indicates escalation cohort, the letter “B” indicates concurrent expansion at lower dose level to obtain additional PK data.
Within Table 14-20, P(Target) NDL represents the probability that the true DLT rate for the dose lies in the target interval (16%, 33%) while P(Over) NDL represents the probability that the true DLT rate for the dose exceeds 33%.

Overall, the model is showing appropriate behaviors, in agreement with clinical sense and decision making process. The dose levels investigated correspond to the provisional dose levels specified in Section 6.2.2.

[redacted]

14.3.3 References (available upon request)

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