NOVARTIS

Clinical Development

NIR178, PDR001

Oncology Clinical Trial Protocol CNIR178X2201 / NCT03207867

A Phase II, multi-center, open label study of NIR178 in combination with PDR001 in patients with selected advanced solid tumors and non-Hodgkin lymphoma

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List of abbreviations

A2aR	Adenosine A2a Receptor
ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibody
AE	Adverse Event
AhR	Arylhydrocarbon receptor
ALK	Anaplastic lymphoma receptor tyrosine kinase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AMP	Adenosine monophosphate
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BID	*bis in diem*/twice a day
BOR	Best overall response
CI	Confidence interval
Cmax	Maximum concentration
CMO&PS	Chief Medical Office and Patient safety
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
CYP	Cytochrome P450
DBL	Database lock
DC	Dendritic cell
DCR	Disease control rate
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLBCL	Diffuse large B cell lymphoma
DLT	Dose Limiting Toxicity
DOR	Duration of response
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
FCT	Film-coated Tablet
FDA	Food and drug administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal

[redacted]

GM-CSF	Granulocyte-macrophage colony-stimulating factor
HGC	Hard gelatin capsule
HIV	Human immunodeficiency virus (HIV)
HNSCC	Head and neck squamous cell carcinoma
HSV	Herpes simplex virus
IA	Interim analysis
IC	Non-tumor immune cell staining score
IFNγ	Interferon gamma
ILD	Interstitial lung disease
IL-6	Interleukin-6
INR	International Normalized Ratio
irAEs	Immune-related adverse events
iRECIST	Immune-related response evaluation criteria for solid tumors (RECIST)
IRT	Interactive Response Technology (Interactive Web Response System)
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous(ly)
LFT	Liver function test
LLOQ	Lower Limit of Quantification
mCRPC	Metastatic Castration Resistant Prostate Cancer
M-CSF	Macrophage colony-stimulating factor
MRI	Magnetic resonance imaging
MSS	Microsatellite stable
MTD	Maximum tolerated dose
NGS	Next-generation sequencing
NK	Natural killer cell
NSCLC	Non-small cell lung cancer
OATP	Organic anion transporting polypeptide
ORR	Overall response rate
OS	Overall survival
PAS	Pharmacokinetic analysis set
PBMC	Peripheral blood mononuclear cell
PCWG3	Prostate Cancer Working Group 3
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS	Progression free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PR	Partial response
PSA	Prostate-specific antigen
PT	Prothrombin time
PxR	Pregnane X Receptor
Q2W	Every two weeks
Q4W	Every 4 weeks
RCC	Renal cell carcinoma

[redacted]

RDE	Recommended dose for expansion
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RoW	Rest of the world
RP2D	Recommended phase II dose
S1	Schedule 1
S2	Schedule 2
S3	Schedule 3
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SJS	Stevens-Johnson syndrome
TBIL	Increased total bilirubin
TCGA	Tumor Cell Genome Atlas
Teffs	Effector T cells
TEN	Toxic epidermal necrolysis
TIL	Tumor infiltrating lymphocytes
TKI	Tyrosine-kinase inhibitor
Tmax	Time to reach maximum (peak) drug concentration
TNBC	Triple Negative Breast Cancer
Tregs	Regulator T cells
TTF	Time to treatment failure
TTP	Time to progression
ULN	Upper Limit of Normal

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
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Personal data	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.
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) 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 patient permanently stops taking study treatment for any reason

[redacted]

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

[redacted]

Amendment 06 (22-Oct-2020)

Amendment rationale

The primary purposes of this protocol amendment are:

1) To open Part 3 of the study to explore the clinical activity of treatment with PDR001 + NIR178 in patients with TNBC whose disease does not express PD-L1 IC=0 (<1%) as determined by VENTANA PD-L1 SP142 Assay. Additionally, to assure a more homogenous patient population, patients must not have received more than 2 prior lines of chemotherapy for advanced or metastatic disease. Evidence of clinical activity was observed in heavily pretreated TNBC patients in Part 1 of this study, with an ORR of 11% in 27 evaluable patients who received NIR178 160 mg BID plus PDR001 400 mg Q4W. In a subset of patients, we observed the 2 PR and 1 SD in 4 patients with a PD-L1 SP-142 IC=0. With the recent approval of PD-(L)1 inhibitors in combination with nab-paclitaxel for patients with advanced or metastatic TNBC, whose tumors express PD-L1 (IC≥1) (Schmid et al 2018, Narayan et al 2020), an effective treatment for patients with immunologically cold tumors is needed.
2) To introduce a new film-coated tablet (FCT) formulation of NIR178 into Part 3 of the study only. The available PK data from this study, using a hard gelatin capsule formulation of NIR178 consistently shows large variability in drug exposure in patients. Based on preclinical PK studies for formulation conducted in Beagle dogs, the alternative FCT formulation is expected to enhance the oral bioavailability of NIR178 in humans and reduce variability in PK. Furthermore, the new FCT offers more favorable biopharmaceutical properties compared to the existing capsule formulation, including smaller pill size, presence of a film coat, and availability of a higher dosage strength (240 mg) of NIR178 to reduce pill burden. The other parts of the study will continue to use the hard gelatin capsule formulation of NIR178.

Additional changes include:

Reduction in the ECG collection plan to safety monitoring levels. As of 03 Aug 2020, extensive ECG sampling, with time-matched PK data, was performed in 257 patients in the CNIR178X2201 study including 244 patients at NIR178 160mg BID, and 13 patients at NIR178 240mg BID; both in combination with PDR001 400mg Q4W. Two out of 257 (<1.0%) patients experienced QTc prolongation (one G1 and one G2) suspected to be related to study treatment. Formal PK-QTc analysis is currently ongoing.

Amendment of the safety run-in to assess NIR178 240mg BID in combination with PDR001 400mg Q4W starting at Cycle 1 in Japanese patients. No obvious ethnic differences in safety and PK were observed between Japanese versus non-Japanese patients and no DDI between NIR178 and PDR001 was observed. Therefore, patients in the Japanese safety run-in will receive this investigational combination therapy starting at Cycle 1.

Revision in the definition of end of study to include the option for patients 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.

[redacted]

Addition of potential drug-induced liver injury (DILI) follow-up guidance based on a Health Authority request. Further recommendations for dose reduction and follow up for DILI and pneumonitis have been added. To date, no Hy's law cases or death cases due to hepatic adverse events have been reported.

Study Status

As of August 3rd, 2020 a total of 266 patients were treated in the study. In Part 1, 198 patients were treated: RCC, mCRPC, TNBC, DLBCL, HNSCC, Melanoma, MSS Colorectal Cancer, Pancreatic, Urothelial. In Part 2, 62 NSCLC patients were treated: Schedule 1 (22), Schedule 2 (20) and Schedule 3 (20). Part 2 of the study is now closed to enrollment. In the Japanese safety run-in, 6 patients were treated: NIR178 single agent 80mg (3) and NIR178 single agent 160mg (3) during Cycle 1.

Changes in 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:

- Protocol summary: Updated to indicate that Part 3 will be opened in parallel with Part 1 to further assess TNBC patients with PD-L1 SP142 IC score of 0 using NIR178 continuous dosing schedule in combination with PDR001. Clarified that a second tumor group will be considered for Part 3 after completion of Part 1. Additional updates to this section include the following: all newly enrolled Japanese patients beginning with this amendment will receive 240mg of NIR178 (in combination with PDR001 400mg Q4W) as part of the safety run-in, the addition of a new FCT formulation of NIR178 to evaluate the pharmacokinetics and safety in comparison to the current capsule formulation and the addition of TNBC to one of the selected tumor types in Part 3.
- Section 1.2.1.3 Biopharmaceutics: A section was added to provide relative bioavailability data in Beagle dogs for NIR178 existing capsule formulation versus NIR178 film-coated tablet and suspension formulation. Table 1-1 added to provide aforementioned data.
- Section 1.2.1.4 Clinical experience: Updated the cut-off date to align with the latest NIR178 (PBF-509) Investigator's Brochure edition 4. Removed a DLT that was inadvertently included. Added study status update in regards to CNIR178X2201.
- Section 2.2 Rationale for the study design: Updated to reflect that Part 3 will be opened in parallel with Part 1 and will enroll TNBC patients with PD-L1 SP-142 IC score of 0 (<1%) as part of one of the selected tumor groups. Additionally, Part 3 will assess the safety and pharmacokinetics of a new FCT formulation of NIR178 at the dose of 160 mg BID using a continuous dosing schedule. Additional clarifications include the use of NIR178 240mg BID in combination with PDR001 in Japanese patients as part of the safety run-in part.
- Section 2.3 Rationale for dose regimen selection: Updated the dosing regimen of the Japanese safety run-in to NIR178 240mg BID in combination with PDR001 starting at Cycle 1 Day 1. Additional updates include clarifying Part 3 enrollment dose with the FCT formulation of NIR178 as well as rationale for why the formulation was selected.

[redacted]

- Section 2.6 Risks and Benefits: A statement was added to note that no new safety risks due to the SARS-CoV-2 virus and the COVID-19 pandemic have been identified at this time and therefore the benefit risk of study treatment remains unchanged.
- Table 3-1 Objectives and endpoint: Updated to include PDR001 plasma concentrations and PK parameters as a secondary objective for the Japanese safety run-in part of the study.
- Section 4.1 Description of study design: Updated to clarify that Part 3 will be opened in parallel with Part 1 and will assess TNBC patients with a known PD-L1 SP-142 status of IC=0 (<1 %) using the FCT formulation of NIR178. Additionally, explanation was added that Part 3 will explore the safety and pharmacokinetics of the FCT formulation of NIR178.
- Figure 4-1 Study design: Added TNBC with PD-L1 SP142 status of IC=0 (<1 %) as one of the selected tumor groups of Part 3. Additionally, updated Part 3 study design and included language for NIR178 240mg in combination with PDR001 in the Japanese safety run-in.
- Figure 4-2 Study Design Japanese run-in part: Updated figure to reflect current Japanese safety run-in design
- Section 4.1.3 Part 3: NIR178+PDR001 additional exploration in selected tumor types: Updated to clarify that one of the tumor groups selected for Part 3 will include TNBC. Additionally, dose increment criteria for Part 3 was added.
- Section 4.1.4 Japanese safety run-in part: Revised language to state that as of Amendment 6 patients enrolled in the Japanese safety run-in will receive NIR178 240mg BID in combination with PDR001. Additional updates include adding the 240mg dose level to the DLT period language.
- Section 4.3 Definition of end of study: Added language for post-trial access programs or roll over protocols which would allow all ongoing patients to transfer to that clinical study as applicable.
- Section 5.2 Inclusion criteria: Added TNBC with PD-L1 status of IC=0 (<1%) as determined by Ventana PD-L1 SP-142 assay as one of the selected tumor groups of Part 3. Additionally, inclusion criteria for Part 3 TNBC tumor group has been added.
- Section 5.3 Exclusion criteria: Added reference to Appendix 6 which contains the Cockcroft-Gault formula.
- Section 6.1 Study treatment: Updated to note the formulation for Part 3 as NIR178 FCT.
- Table 6-1 Dose and Treatment schedule: Table updated to include a new row for the NIR178 FCT formulation.
- Section 6.1.1 Dosing Regimen: Updated to change the formulation of NIR178 to FCT in Part 3 of the study and clarified that as of Amendment 6, Japanese safety run-in patients will enroll in NIR178 240mg in combination with PDR001. Additional updates include adding language around dose escalation to NIR178 240mg BID FCT.

[redacted]

- Table 6-2 Criteria for dose reduction/interruption and re-initiation of NIR178 and PDR001 treatment for adverse drug reactions: Revised to include recommended dose modifications for DILI. Additional updates for pneumonitis section include recommending to seek consultation with pulmonologist and managing toxicity per institutional practice. Additionally, updated recommendations were added for AST/ALT elevation management. Guidance provided if suspicion of autoimmune hepatitis due to AST/ALT elevation is noted.
- Section 6.2.2.1 Follow up on potential drug-induced liver injury (DILI) cases: Included additional guidance on DILI follow-up.
- Table 6-4 Clinical and Diagnostic assessments to rule out possible causes of LFT abnormalities: Added table to provide guidance on specific assessments that can be performed in the event of LFT abnormalities.
- Table 6-5 Dose reduction steps for NIR178: Additional table added to note dose reduction steps for patients receiving NIR178 FCT in Part 3 of the study. Additionally, the dose reduction table for NIR178 160mg BID was removed as dose reduction steps are outlined in the NIR178 capsule formulation (hard gelatin capsule) respective table.
- Section 6.3.2 Permitted concomitant therapy requiring caution and/or action: Added language that BCRP substrates in combination with NIR178 should be used with caution.
- Section 7.1 Study flow and visit schedule: Clarified that Part 3 will follow the continuous BID visit schedule. Additional clarification was added that allows the implementation of alternative care if the COVID-19 pandemic limits or prevents on-site study visits.
- Table 7-1: Visit evaluation schedule for patients in Part 1, Part 2 NIR178 S1 (NIR178 Schedule 1-BID continuous dosing), Part 3 and Japanese safety run-in: Added row to note that baseline tumor molecular characteristics for patients will be collected at screening.
- Section 7.1.1.3 Patient demographics and other baseline characteristics: Added clarification that baseline tumor molecular characteristics may be collected to determine eligibility of inclusion in the study.
- Section 7.1.3 Discontinuation of study treatment: Language added that end of treatment procedures will be performed for patients who transfer into another study or alternative treatment.
- Section 7.1.5.1 Follow-up period: Section added to clarify that patients enrolled to another clinical study or alternate treatment as described in Section 4.3 will not have follow-up for safety, disease progression and survival assessments performed.
- Section 7.2.2 Safety and tolerability assessments: Language added that regular phone or virtual calls will occur every 4 weeks or more frequently if needed for safety monitoring during the COVID-19 pandemic if on-site study visits are limited/prohibited.
- Table 7-6 Local clinical laboratory parameters collection plan: Added activated partial thromboplastin time (aPTT) test name to the coagulation test category.
- Section 7.2.2.5.7 Pregnancy and assessments of fertility: Language added to state if during the COVID-19 pandemic the patient cannot visit the site to have serum pregnancy tests, local urine pregnancy test kits may be used.

[redacted]

- Table 7-7 Central ECG collection plan: Reduced the ECG collection plan at selected visits to safety monitoring levels.
- Section 7.2.3 Pharmacokinetics and immunogenicity assessments: Statement added to note that if during COVID-19 visits are limited, the collection of samples may be modified by Novartis.
- Table 7-8 Pharmacokinetic blood collection log for PDR001 and ADA (all study parts and schedules, including Japanese safety run-in and Part 3): clarification added for patients enrolled in the Japanese safety run-in part as of amendment 6 will receive NIR178 in combination with PDR001 starting at cycle 1 and PDR001/ADA PK sample collections will also begin at Cycle 1.
- Table 7-9 Pharmacokinetic blood collection log for NIR178: Part 1, Part 2, Part 3 (NIR178 Schedule 1), and Japanese safety run-in: clarification added to table header to include Part 3 into NIR178 PK collection log table.
- Section 9.4 Database management and quality control: Removed language noting a CD-ROM of patient data would be given to Investigators after final database lock.
- Section 10.4.1 Variable: Minor typographical error was removed and included in appropriate Section 10.5.2.
- Section 10.4.2 Statistical hypothesis, model, and method of analysis: Updated to indicate that Part 3 will enroll TNBC as one of the selected tumor groups and how TNBC data will be analyzed.
- Section 10.8 sample size calculation: Updated to clarify that 20-30 patients will be enrolled in Part 3. Table 10-6 and Table 10-7 added for further clarification. Additional updates include adding NIR178 in combination with PDR001 to the Japanese safety run-in part. Section 11.3 Informed Consent procedures: Language was added that if challenges arise during the COVID-19 pandemic and limit obtained written informed consent, informed consent discussion may occur remotely based on local guidance.
- Section 13 References: Updated to reflect new references
- Appendix 1: Concomitant Medications: Updated the concomitant medication reference and Table 14-1 List of Prohibited Medications and Table 14-2 List of Medications to be used with caution.
- Section 14.2.30 End of treatment phase completion: Updated the end of treatment visit and its associated assessments to occur within 14 days of last study treatment.
- Appendix 6 Calculation – Cockcroft-Gault formula for GFR estimate: Calculation guidance added

IRBs/ECs

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

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

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

[redacted]

Amendment 05 (November 2019)

Amendment rationale

The primary purpose of this protocol amendment is to increase the dose of NIR178 to 240 mg twice daily from 160 mg twice daily for all newly enrolled patients, as well as to allow the enrollment of patients with metastatic castration resistant prostate cancer (mCRPC) and IO pretreated RCC patients in Part 1 of the study.

The rationale to increase the dose of NIR178 to 240 mg twice daily is based on:

1. Data from the Phase I/Ib clinical trial, CNIR178X2103J, where the maximum tolerated dose (MTD) of NIR178 was determined to be 240 mg BID in combination with PDR001 400 mg Q4W. In the current study, as of May 24, 2019, 224 patients have been treated safely with NIR178 160 mg twice daily in combination with PDR001 400 mg Q4W (please refer to Section 2.3 for details) to support increasing the NIR178 dose to 240 mg BID.
2. Preliminary exposure response data [redacted] analysis from available paired biopsies in patients treated with NIR178 in the CNIR178X2201 study demonstrated that post-treatment increases in CD8 T cell tumor infiltration relative to baseline (measured by IHC) were associated with improved anti-tumor activity. The extent of CD8 infiltration in the tumor also correlates with systemic exposure. Therefore, increasing the dose of NIR178 to 240 mg BID would be expected to translate into improvement in clinical response rates (please refer to Section 2.3 for details). The dose of the combination partner PDR001 remains unchanged (400 mg every 4 weeks).

A new tumor type will be added to Part 1 to allow enrollment of patients with mCRPC based on emerging clinical data supporting a potential role for adenosine pathway immune modulation in this setting. Anti-CD73 monoclonal antibody treatment suppressed growth of prostate tumors and inhibited lung metastases in mice inoculated with TRAMP-C1 tumor cells (Stagg et al 2012). Emerging clinical data support a potential role for adenosine pathway immune modulation in patients with mCRPC (Siu et al 2018, Bendell et al 2019, Luke et al 2019).

A new tumor group of IO pretreated RCC patients will now be enrolled into the RCC arm of Part 1 of the study since immune checkpoint inhibitors are now routinely used in the treatment of advanced/metastatic RCC and have resulted in significantly longer overall survival. Nevertheless, disease progression is still observed in a large proportion of patients who develop resistance to checkpoint inhibitors. In order to test the hypothesis that immunosuppression due to activation of the adenosine pathway leads to resistance to anti-PD-(L)1 therapy and treatment with NIR178 may reverse this resistance, the inclusion criteria will be amended to include RCC patients who have been previously treated with anti-PD-(L)1 therapy.

Since the use of checkpoint inhibitors has become first line standard of care treatment for indications, (such as NSCLC, RCC) the design of Part 3 of the protocol will be modified to allow for further evaluation of one or two tumor groups (from Part 1 and Part 2). Once the recommended dose and dosing schedule (Part 2) is determined, Part 3 may be initiated after agreement among Novartis and investigators.

[redacted]

There has not been much hypothesis or evidence either from this trial (or in the literature) regarding changes in tumor mutational burden over the course of the few months on therapy. The on treatment cfDNA collections have been of value in the case of trials (usually for targeted therapies) with a goal of monitoring the timing of specific acquired resistance mutations. [redacted]

Study Status

At the time of this amendment, November 14, 2019, a total of 243 patients have been enrolled on the study. In Part 1, 174 patients have been enrolled: RCC (11), TNBC (30), DLBCL (9), HNSCC (23, including 4 non-HNSCC), Melanoma (16), MSS Colorectal Cancer (58), Pancreatic (14), Urothelial (14). In Part 2, 62 NSCLC patients were enrolled: Schedule 1 (22), Schedule 2 (20) and Schedule 3 (20). In Japanese safety run-in, there were 6 patients enrolled: NIR178 80mg (3) and NIR178 160mg (3).

Changes in 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:

- Protocol Summary: updated to allow Part 3 to enroll patients in any one or two tumor groups based on emerging clinical data from Part 1 and Part 2. Additional updates to this section include the following: all newly enrolled patients beginning with this amendment will receive 240 mg of NIR178 (in combination with PDR001 400 mg Q4W), the addition of mCRPC and IO pretreated RCC to the tumor types in Part 1 and the removal of language requiring a protocol amendment to open Part 3 for enrollment.
- Section 1.2.1.3 Clinical experience: updated to reflect that the MTD of the CNIR178X2103J study for NIR178 as a single agent was declared as 480 mg BID and the MTD for NIR178 in combination with PDR001 400 mg Q4W was declared as 240 mg BID.
- Section 2.2 Rationale for the study design: updated to reflect that Part 3 will include any one or two tumor groups based on emerging clinical data from Part 1 and Part 2, as well clarify that if NSCLC is selected as a tumor group for Part 3, this group will enroll patients previously exposed to immunotherapy. Additional clarifications include that the terms “tumor groups” and “tumor types” are used interchangeably throughout the protocol.
- Section 2.3 Rationale for dose regimen selection: updated the starting dose of NIR178 to 240mg BID for all newly enrolled patients beginning with this amendment as well as the rationale for the dose change, which is based on combined PK [redacted] data along with exposure-response analysis and data from the ongoing CNIR178X2103J study.
- Table 3-1 Objectives and endpoints: revised to include PCWG3 criteria as a primary endpoint in Parts 1 and 3 as well as PSA as a secondary endpoint for mCRPC. [redacted]
- Section 4.1 Rationale for study design: updated to clarify that Part 3 will open for enrollment after data from Parts 1 and 2 are available

[redacted]

- Figure 4-1 Study design: Added IO pretreated RCC and mCRPC as additional tumor groups to Part 1 of the study. Additionally, updated Part 3 study design
- Section 4.1.1 Part 1: Bayesian adaptive signal finding in solid tumors and DLBCL: added RCC to the IO pre-treated groups as well as mCRPC in Part 1.
- Section 4.1.3 Part 3: NIR178+PDR001 schedule exploration in additional tumor types: updated to clarify that the tumor groups selected for Part 3 will be based on emerging clinical data from Parts 1 and 2. If NSCLC is selected as a tumor group for Part 3, this group will enroll patients previously exposed to immunotherapy.
- Section 4.1.4 Japanese Safety Run-In Part: Added Japanese safety run-in results for the 80 mg and 160 mg doses of NIR178
- Section 4.4 Early Study Termination: updated template language for early termination of the trial
- Section 5.2 Inclusion criteria: updated Part 3 inclusion criteria to clarify that the tumor groups selected for Part 3 will be based on emerging data from Parts 1 and 2, latest scientific literature as well as a discussion between Novartis and study investigators. Additionally, if NSCLC is selected as a tumor group for Part 3, patients who have been exposed to prior immunotherapy will be enrolled. Other updates to this section include the addition of prior lines of therapy requirements for RCC (IO pretreated) and mCRPC.
- Section 5.3 Exclusion Criteria: Added language to allow GnRH therapy for mCRPC patients.
- Section 6.1 Study treatment: updated to change the dose of NIR178 to 240 mg BID for all newly enrolled patients.
- Section 6.1.1 Dosing regimen: updated to change the dose of NIR178 to 240 mg BID for all newly enrolled patients.
- Section 6.1.3 Treatment duration: Added language regarding PCWG3 guidance for mCRPC
- Table 6-4 Dose reduction steps for NIR178: revised to include an additional table indicating the dose reduction steps for newly enrolled patients starting on the study at the 240 mg dose.
- Table 7-1, Table 7-2 and Table 7-3 Visit schedule and assessments: revised to only require CrCl calculation at Screening and Cycle 1 Day 1, included aPTT for coagulation testing and only required a pregnancy test for women of child-bearing potential. [redacted]
- Section 7.1.2 Treatment period: Added PCWG3 guidance for mCRPC
- Section 7.1.3 Discontinuation of study treatment: Added PCWG3 guidance for mCRPC
- Section 7.1.6 Follow-up for disease progression: Added PCWG3 guidance for mCRPC
- Section 7.2.1 Efficacy assessments: Added PCWG3 guidance for mCRPC
- Table 7-4 Imaging/Disease assessment collection plan: Added language for additional imaging bone scans for mCRPC

[redacted]

[redacted]

- Section 10.4 Primary objective: updated to reflect that Part 3 will enroll one or two tumor groups based on emerging data from Parts 1 and 2 as well as remove the requirement of a protocol amendment in order to open Part 3
- Section 10.4.2 Statistical hypothesis, model, and method of analysis: updated to indicate that Part 1 will enroll patients in 13 different groups. Additional updates include clarifying that the tumor groups selected for Part 3 will be based on emerging data from Parts 1 and 2 and if NSCLC is selected as a tumor group for Part 3, patients who have been exposed to prior immunotherapy will be enrolled
- Section 10.5.1 Efficacy objectives: PSA was added for mCRPC patients
- Table 10-1 Type of tumors of interest with definition of being clinically meaningful: updated to include IO pretreated RCC as a tumor group in Part 1 as well as mCRPC.
- Section 10.8 Sample size calculation: updated the sample size for all tumor types. Additionally updated to include that the tumor groups selected for Part 3 will be based on emerging data from Parts 1 and 2 and if NSCLC is selected as a tumor group for Part 3, patients who have been exposed to prior immunotherapy will be enrolled.
- Section 13 References: Updated to reflect new references
- Section 14.4.1.1: Corrected variance parameter typo
- Section 14.4.5: Added RCC IO pretreated group as well as mCRPC group to the statistical section regarding modeling
- Appendix 5 Efficacy guideline for prostate cancer: Section Added – PCWG3 guidance

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

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

[redacted]

Amendment 4 (29-Oct-2018)

Amendment rationale

The primary purpose of this amendment is to update the protocol eligibility criteria and related statistical analysis sections for select indications from Part 1 based on preliminary evidence of anti-tumor activity and changes in the standard of care, specifically:

MSS CRC:

- Based on the available clinical data in this indication (1 patient with a partial response and 3 with stable disease out of 14 evaluable patients), patients with microsatellite stable colorectal cancer (MSS CRC) will continue to be enrolled. However, in order to evaluate efficacy and safety for patients with different RAS genotypes, enrollment will continue in two sub-groups (RAS wild-type & RAS mutant) based on locally available laboratory data. Moreover, RAS status will be collected, including for patients that have already been enrolled, as per standard local clinical practices.

Head & Neck:

- Based on the available clinical data in this indication (2 patients with partial responses and 3 with stable disease out of 11 evaluable patients), patients with Head and Neck group cancer will continue to be enrolled. However, enrollment will be restricted to Head and Neck Squamous Cell Carcinoma (HNSCC), thus creating a more homogenous patient population.
- Recent publications points towards a role of the A2aR/CD73 axis during cancer progression and overall survival in HNSCC (Vogt et al 2018). In order to explore if the adenosine pathway is critical in the acquired resistance to an anti-PD1/L1therapy, a new treatment group with HNSCC who were previously treated with an anti-PD1/L1 antibody as a single agent or in combination will be included.

Cutaneous Melanoma:

- In order to evaluate a homogenous melanoma patient population, only cutaneous melanoma patients will be enrolled. Checkpoint (anti PD-1) and BRAF V600 inhibitors have become the standard of care for cutaneous melanoma. To test the hypothesis that adenosine pathway inhibition could help bypass acquired resistance to anti-PD(L)1 therapy, the inclusion criteria will be amended to require patients have been treated with prior anti-PD(L)1 therapy and BRAF V600 inhibitor therapy (for BRAF V600 mutant patients). The BRAF status will be determined per standard local laboratory testing.

Other updates to the protocol:

- The contraception language has been updated to align with the latest version of the PDR001 and NIR178 Investigator Brochures. A condom is not required to be used while receiving monoclonal antibodies (e.g. PDR001 in this case only) as they are not genotoxic and they have a low distribution to the semen with a relatively small quantity of semen delivered to the vagina (low absorption). Hence, sexually active males should still use a condom during intercourse while on study treatment and 30 days after stopping NIR178. Patients should not father a child during this period.

- To facilitate the work flow of the participating sites and offer more flexibility particularly on days with extensive PK draws for both, NIR178 and PDR001, and ECG assessments (e.g. Cycle 1 Day 1), the 60 minutes window between NIR178 morning dose and start of PDR001 infusion has been lifted since this is not anticipated to affect PK property determination for either drug.
- An optimized LC-MS/MS assay permits measurement NIR178 and its metabolite NJI765 simultaneously using a single plasma sample, therefore the collection of separate blood aliquots to assess PK of the metabolite has been removed. The metabolite will continue to be monitored in participating patients using NIR178 PK sample aliquots.
- Scan assessments post discontinuation of study treatment will no longer be collected when the patient starts a new antineoplastic therapy
- An optional biopsy may be collected for patients that continue study treatment beyond disease progression due to overall clinical benefit.
- Minor updates to the permitted and prohibited concomitant therapy tables to ensure that the same drug does not appear in both tables of the protocol. In addition, update to the list of drugs with known risk of QT prolongation/TdP under prohibited medications table based most recent database from CredibleMeds®.
- Removal of the blood sample collection for the assessment of serum cytokines used for retrospective analysis of a cytokine release syndrome adverse event. Blood samples for serum cytokines were included due to the unknown risk of CRS with IO agents alone and in combination, and to allow an assessment of any association between cytokines and clinical events. These samples have been drawn at baseline and at the time of a potential CRS event, stored, and analyzed retrospectively. Due to this, results are not intended to be used to support clinical decision-making for patients with possible CRS. There were no unexpected clinically assessed events of CRS observed across 19 studies including more than 2200 patients. The risk of CRS in the current study is deemed to be low, thus supporting the removal of this blood sample collection.

Study status

At the time of this amendment, a total of 115 patients have been enrolled on the study.

Changes in 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 1.2.1.3 Clinical experience has been updated based on available data for the CNI178X2103J trial.
- Section 2.1 Study rationale and purpose: revised based on updated data available for CNIR178X2103J trial.
- Section 4.1 Description of study design: revised to add a sentence on optional biopsy may be collected at disease progression for patients continuing on study treatment due to overall clinical benefit.
- Figure 4-1 Study Design: was updated based on the new template and addition of new tumor types

[redacted]

- Section 4.1.1 Part 1: Bayesian adaptive signal finding in solid tumors and DLBCL: revised to include the additional tumor types
- Section 4.2.1 Part 1: Bayesian adaptive signal finding in solid tumors and DLBCL: revised to include 40 MSS CRC patients
- Section 5.2 Inclusion Criteria #4:
  - RAS mutant: Up to three prior lines of therapy for metastatic disease including prior therapy with fluoropyrimidine- oxaliplatin- and irinotecan- based regimens.
  - RAS wild type: Up to three prior lines of therapy for metastatic disease including prior therapy with fluropyrmidine-oxaliplatin- and irinotecan-based regimens along with prior treatment with an antibody targeting EGFR (e.g. cetuximab or panitumumab).
- Section 5.2 Inclusion Criteria #4:
  - IO Naive HNSCC: Patients with squamous cell carcinoma of head and neck (HNSCC) with no more than 3 prior lines of therapy. Patient must have received a prior platinum-containing regimen and have not been previously treated with any anti-PD1/L1 agents in single agent/combinations.
  - IO pre-treated HNSCC: Patients with HNSCC with no more than 2 prior lines of therapy. Patient must have received a prior platinum-containing regimen and have been pretreated with an anti-PD-1/PD-L1 as a single agent or in combinations
- Section 5.2 Inclusion Criteria #4:
  - BRAF V600 wild type patients: anti-PD-1/PD-L1 single-agent, or in combination with anti-CTLA-4 therapy
  - BRAF V600 mutant patients: anti-PD-1/PD-L1 single-agent, or in combination with anti-CTLA-4 therapy. In addition, subjects must have received prior BRAF V600 inhibitor therapy, either single-agent or in combination with a MEK inhibitor
- Section 5.2 Exclusion criteria #9: revised prior lines of therapy based on each tumor type
- Section 5.3 Exclusion Criteria #32: The contraception language has been updated to align with the latest version of the PDR001 and NIR178 Investigator Brochures.
- Section 6.1 Study Treatment: The start time of PDR001 infusion on dosing days can occur at any given time regardless of the dose administration schedule of NIR178. The requirement for 60 minute window between NIR178 morning dose and start of PDR001 infusion in inpatient visits in which the two study drugs are administered on the same day (e.g., Cycle 1 Day 1, Cycle 2 Day 1, etc) has been removed to facilitate the work flow of the participating sites, since this is not predicted to affect the PK properties of either drug.
- Section 6.2.2 Follow-up for toxicities: removal of safety cytokine analysis assessment
- Section 7.1 Study flow and visit schedule: Tables 7-1, 7-2, and 7-3 have been updated to reflect that the safety cytokine assessments are no longer required.
- Section 7.1.4 Withdrawal of Consent language has been updated
- Section 7.1.6 Follow-up for Disease Progression: Once patients start on new antineoplastic therapy post discontinuation of study treatment, patient does not need to be followed for disease progression.

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- Section 7.1.7 Survival Follow-Up: Clarified that survival follow-up will start upon completion of the 150-day safety follow-up or disease progression follow-up
- Section 7.2 Pharmacokinetics and Immunogenicity: An update on the PK sample collection plan has be done, removing the collection of separate blood samples to measure NJI765 (NIR178 metabolite), since a new assay allows to measure both molecules (NIR178 and NJI765) from the same blood sample.
- Section 7.2.2.7.1 Electrocardiogram (ECG): The interval for ECG collection has been updated from 5-10min to 1-2min to ensure consistency throughout the protocol
- Section 7.2.3 Pharmacokinetics and immunogenicity assessments: revised to include language regarding if PDR001 is stopped or temporally paused, the events should be captured in the DAR PK eCRF pages.
- Table 7-9 Pharmacokinetics blood collection log for NIR178 Part 1: have been revised stated that the same blood samples collected to asses PK of NIR178 will be used to measure its metabolite NJI765
- Table 7-10 Pharmacokinetics blood collection log for NIR178 Part 2: have been revised stated that the same blood samples collected to asses PK of NIR178 will be used to measure its metabolite NJI765
- Table 7-11 Pharmacokinetics blood collection log for NIR178 Part 3: have been revised stated that the same blood samples collected to asses PK of NIR178 will be used to measure its metabolite NJI765
- Section 7.2.31 Analytic methods: revised text regarding quantification of PK collection or NIR178 and NJI765 samples
- Section 8.4 Pregnancies: Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study and the newborn will be followed up to 12 months (instead of 3 months) after delivery date.
- Section 10 Statistical Methods & Data Analysis: Section has been updated accordingly
- Section 14.1 Appendix 1 Concomitant Medications: The permitted and prohibited concomitant therapy tables has been updated to ensure that the same drug is not listed in both tables of the protocol
- Section 14.4 Appendix 4 Details regarding the statistical methodology: section has been 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 other changes described in this amended protocol require IRB/IEC approval prior to implementation.

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

Amendment 3 (02-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) in response to the occurrence of a case of Stevens Johnson Syndrome in the current study. 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 the criteria for dose reduction/interruption and re-initiation of treatment for adverse drug reactions and, in addition, aligning with the recently published guidelines on the clinical management of suspected immune-related toxicities.

Study status

At the time of this amendment, a total of 110 patients have been enrolled on the study.

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 2.6: Risk-benefit section was updated to reflect the overall safety risk including cutaneous toxicity. In addition, reference to the dose modification guidelines was added
- Table 6-2 The criteria for dose reduction/interruption and re-initiation of treatment for adverse drug reactions: language has been added to mandate permanent study treatment discontinuation for SJS/TEN (USM related)
- Table 6-2 The criteria for dose reduction/interruption and re-initiation of treatment for adverse drug reactions were updated to include latest toxicity management guidelines per ASCO, NCCN and ESMO. Moreover, the AST and ALT exclusion criteria has been revised to align with the updated toxicity management guidelines
- Appendix 5- Recommended management algorithms for suspected toxicities and all references to Appendix 5 have been removed as the information is now incorporated in Table 6-2 for dose reduction/interruption and re-initiation of treatment for adverse drug reaction

[redacted]

IRBs/IECs

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

The changes in this amendment identified above as being related to the USM have already been implemented by a USM letter issued on 18 May 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.

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

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

Amendment 2 (29-Aug-2017)

Amendment rationale

The primary purpose of this amendment is to implement the following changes:

- Inclusion of Japanese patients via safety run-in part in order to evaluate safety and pharmacokinetic properties of NIR178 as a single agent prior to their participation in different parts of this study, as recommended by the Japanese Health Authority. The Japanese safety run-in part will enroll separately from the phase II study in the rest of the world (RoW).
  Since there were no differences in the safety and PK profiles of PDR001 between Japanese and non-Japanese patients treated at the RDE of 400mg IV Q4weeks in study CPDR001X1101, and given the low likelihood of drug-drug interaction (DDI) between NIR178 and PDR001 (Section 2.4.1), the safety and PK profile of single agent NIR178 in Japanese patients compared to that for patients treated in the ongoing phase 1b dose escalation study in NSCLC (CNIR178X2103J), will be the primary determinant of whether or not Japanese patients can join the phase II part of this study. If the dose of NIR178 used in Parts 1-3 (160mg BID continuously) is declared to be tolerable and safe in Japanese patients, then Japanese patients may subsequently be enrolled into all parts of the phase II study. Additional changes specifically applying to Japanese patients in the safety run-in are:
  - added language for Japanese patients that written consent is necessary from both the patient and his/her legal representative if he/she is under the age of 20 years
  - added chest x-rays at screening and during cycle 1 and oxygen saturation during physical exam in order to monitor drug-induced interstitial lung disease (ILD) per Japanese standards
  - For Japanese patients, added the requirement for hospitalization during the first cycle of therapy

[redacted]

- Based on recent Health Authority recommendation, overall response assessment by iRECIST has been added as a secondary endpoint, following the iRECIST definitions and rules for response assessment in cancer immunotherapy trials (Seymour et al 2017)
- irRC criteria has been replaced by iRECIST criteria for guiding decisions on treatment duration and/or discontinuation due to disease progression. Accordingly, patients will receive treatment with the combination of NIR178+PDR001 until disease progression (assessed by investigator per iRECIST)
- Based on the availability of a new capsule strength (40 mg) for NIR178, the first dose reduction step from 160mg (dose level -1) for patients requiring dose reduction due to adverse events has been changed from 80mg (50% dose reduction) to 120mg BID (25% dose reduction), in order to minimize the impact on benefit to the patient. The dose of 80mg NIR178 has been changed to dose level -2
- In order to account for patients who cannot obtain biopsies in cycle 3 due either to early disease progression or early response with loss of accessible residual lesions, the on-treatment biopsy and blood sample collection time point has been moved from C3D15 ± 15 days and C2D1, respectively, to C2D1 +15 days
- Minor inconsistencies and typographical errors have been corrected throughout the document

Study status

At the time of this amendment, the study has not been opened for recruitment.

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.

- Protocol Summary, Table 3-1 Objectives and related endpoints, Section 6.1.3 Treatment duration, Section 7.1.2 Treatment period and Visit evaluation schedule Tables 7-1, Table 7-2, Table 7-3, Section 10.5.1, Appendix 14.3 has been updated to replace irRC with iRECIST published in March 2017. The corresponding term “irRC” was replaced with “iRECIST”.
- Protocol Summary, Section 2.2 Rationale for study design, Table 3-1 Objectives and related endpoints, Section 4.1 Description of study design was updated to include language regarding Japanese safety run-in part. In addition, a new Section 4.1. and a corresponding Figure 4-2 Study design-Japanese run-in part was added to give an overview of the safety in Japanese patients in the run-in part
- Section 5.2 Inclusion criteria: Revised inclusion criteria # 1 to specify consent requirement for Japan
- Section 5.2 Inclusion criteria: Revised inclusion criteria # 2 to specify that the Japanese safety run-in part can enroll in any tumor type included in Part 1 and Part 2
- Section 5.2 Inclusion criteria: Revised inclusion criteria # 3 to exempt patients in the Japanese safety run-in from biopsy requirement as the main purpose of the safety run-in is to evaluate safety and pharmacokinetic property of the study treatment

[redacted]

- Section 5.2 Inclusion criteria: Revised inclusion criteria # 6 to specify that the patients in Japanese safety run-in part may have received prior immunotherapy
- Section 5.3 Exclusion criteria: Revised exclusion criteria # 9 to clarify that the patients in Japanese safety run-in part may have received more than 3 prior lines of therapy
- Section 5.3 Exclusion Criteria: Revised exclusion criteria # 15 to replace QTcB to QTcF
- Section 5.3 Exclusion Criteria: Revised exclusion criteria # 17 to specify history severe hypersensitivity due to ingredients of the study drug(s) another other monoclonal antibodies.
- Section 5.3 Exclusion Criteria: Revised exclusion criteria # 31 to specify women who are considered post-menopausal and not of child bearing potential.
- Section 6.1 Study treatment: Added a new capsule strength (40 mg) for NIR178 in Table in 6-1
- Section 6.1.1 Dosing regimen: Revised to include treatment regimen for Japanese safety run-in part
- Table 6-3 Definitions of dose limiting toxicities for Japanese safety run-in part: Added to include DLT definitions for Japanese safety run-in part
- Table 6-4 Dose reduction steps for NIR178: Revised to add a new dose level -1 (120 mg) for NIR178
- Section 6.4.1 and Section 6.4.2: Updated to clarify that the IRT will not be used for Japanese Safety run-in part.
- Table 7-1 Visit evaluation schedule: Updated to include additional assessments required for Japan (Physical exam at Cycle 2 Day 15, and Chest X-ray at screening, Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 2 Day 15).
- Section 7.1.1 Screening: Updated to revise the biopsy collection window for screening
- Table 7-4 Imaging/Disease assessment collection plan: Updated to add FDG-PET/CT requirement for lymphoma patients with known bone marrow involvement and FDG-avid tumors
- Section 7.2.2.1 Physical examination: Updated to include Japan specific assessments (pulse oximetry)
- Section 7.2.2.6 [For Japan only] Radiological examinations: Added to include Japan specific requirement for Chest X-ray
- Section 7.2.2.7.1 Electrocardiogram (ECG): Clarified that the ECG evaluations will done centrally
- Table 7-8 and Table 7-9 Pharmacokinetic blood collection log for PDR001 and NIR178: Title was updated to include Japanese safety run-in part
- [redacted]
- Section 10 Statistical methods and data analysis, Section 10.5.2.2 Adverse events (AEs): Revised to include analysis plan for Japanese safety run-in part
- Section 10 Statistical methods and data analysis, Section 10.5.1 Efficacy analysis: Updated to include iRECIST as a secondary efficacy endpoint

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes 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 1 (26-May-2017)

Amendment rationale

The primary purpose of this amendment is to address the following health authority requests:

- Clarify that the additional tumor type to be selected in Part 3, based on emerging data from Part 1, may only begin enrollment via implementation by formal protocol amendment
- Update inclusion criteria to require specific prior standard therapies for tumor types in part 1
- Add exclusion criteria for patients with a history of non-infectious pneumonitis or interstitial lung disease
- Add inclusion criteria for DLBCL to ensure that the enrollment of patients with DLBCL is limited to patients with no available therapies of proven clinical benefit
- Provide case definitions for treatment-emergent immune-mediated adverse drug reactions in the protocol and guidance on assessment and management of immune related adverse events
- Include specific criteria for continuing study treatment beyond RECIST-defined radiological progression
- Update risk-benefit section to indicate potential for overlapping toxicities of combination immunotherapies
- Clarify that the primary efficacy analysis will be based on RECIST v1.1 for solid tumors and Cheson 2014 for Lymphoma and that irRC criteria will be used only for decisions around treatment discontinuation due to disease progression

Study status

At the time of this amendment, the study has not been opened for recruitment.

[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 underline for insertions.

- Protocol summary, Section 2.2, Section 4.1.3, Section 10.4, Section 10.8 : Language regarding the "additional tumor type from Part 1" has been modified for Part 3 to specify that the additional tumor type in Part 3 will be selected based on emerging data from Part 1 and enrollment into this tumor group will only occur via a formal protocol amendment.
- Section 2.6 Risks and benefits: Revised to indicate risks of overlapping toxicities for combination immunotherapies
- Section 5.2 Inclusion criteria: Revised inclusion criteria #4 to specify prior lines of systemic therapy for specific tumor type and added inclusion criteria # 5 for patients with DLBCL
- Section 5.3 Exclusion criteria: Added exclusion criteria #5 to exclude patients with history of interstitial lung disease or non-infectious pneumonitis
- Section 6.2.2: Added Section 6.2.2. to define immune related adverse events and management of irAEs
- Section 7.1.2: Updated to clarify criteria for study treatment continuation beyond disease progression
- Section 7.2.1: Clarified that RECIST 1.1 and Cheson (2014) (for DLBCL) will be used for analysis of response. irRC will be used only for treatment decision making around study discontinuation due to progressive disease.
- Section 10.4.1: Updated to clarify that the primary analysis will be based on RECIST v1.1 for solid tumors and Cheson 2014 for DLBCL.
- Section 14.5: Appendix 5 was added to provide recommendation on the management for suspected immune related toxicities

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]

Protocol summary:

Title	A Phase II, multi-center, open label study of NIR178 in combination with PDR001 in patients with selected advanced solid tumors and non-Hodgkin lymphoma
Brief title	Study of efficacy and safety of NIR178 and PDR001 combination in patients with selected solid tumors and non-Hodgkin lymphoma
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this phase II study is to evaluate the efficacy and safety of NIR178 in combination with PDR001 in multiple solid tumors and diffuse large B-cell lymphoma (DLBCL) and further explore schedule variations of NIR178 to optimize immune activation through inhibition of A2aR.
Primary Objective(s) and Key Secondary Objective	The study is divided into 3 parts. The primary objective of each part is as follows: • Part 1:To evaluate the efficacy of NIR178 and PDR001 combination in patients with selected advanced solid tumors and diffuse large B cell lymphoma (DLBCL) • Part 2: To assess the efficacy of several intermittent dosing schedules of NIR178 in combination with PDR001 in NSCLC • Part 3: To further evaluate efficacy of the best performing dosing schedule of NIR178 in one or two tumor groups selected from Part 1 and Part 2. The additional tumor groups will be selected based on the emerging data from Part 1 and Part 2.
Secondary Objectives	• To assess the efficacy of NIR178+PDR001 in select advanced solid tumors and lymphoma • To assess the safety and tolerability of the NIR178 and PDR001 combination • To characterize changes in the immune infiltrate in tumors • To characterize the pharmacokinetics (PK) of NIR178, its metabolite NJI765 and PDR001 in combination • To assess immunogenicity of PDR001 • Japanese safety run-in part: To assess the safety and pharmacokinetic profiles of NIR178 single-agent and in combination with PDR001 in Japanese patients
Study design	This is a multi-center, open label, phase II study to evaluate efficacy of the NIR178 and PDR001 combination in NSCLC, other solid tumors, and diffuse large B-cell lymphoma (DLBCL). The study has three parts: Part 1: Multi-arm Bayesian adaptive signal finding design in solid tumors and diffuse large B cell lymphoma (DLBCL); Part 2: NIR178 schedule exploration in NSCLC; Part 3: Further evaluation of intermittent dosing schedules of NIR178 in combination with PDR001 in additional tumor types, if Part 2 identifies an intermittent dosing schedule of NIR178 as warranting further exploration. In addition, a separate safety run-in part will be conducted for patients in Japan in order to evaluate safety and pharmacokinetics of NIR178 as a single agent and NIR178 in combination with PDR001 prior to their participation in different parts of this phase II study, as recommended by the Japanese Health Authority. This Japanese safety run-in part will enroll separately from the phase II study in the rest of the world (RoW). Patients enrolled in this study will receive NIR178 160 mg either BID continuously or based on the assigned intermittent dosing schedule. All newly enrolled patients under Amendment 5 will receive NIR178 240 mg BID. PDR001 will be administered via IV infusion over 30 minutes once every 4 weeks. Each treatment cycle is 28 days. As of protocol amendment 6, Part 3 will be opened in parallel with Part 1 to further assess TNBC patients with a PD-L1 SP-142 IC score of 0 (<1%) using the NIR178 continuous dosing schedule in combination with PDR001. A second tumor group will be considered for Part 3 after completion of Part 1. Patients will receive treatment with the combination until disease progression (assessed by investigator per immune-related response criteria (iRECIST) (Appendix 3 or Cheson et al (2014)),

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	unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator), otherwise known as End of Treatment.
Population	Adult patients with histologically documented advanced or metastatic solid tumors (e.g. non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), pancreatic cancer, urothelial cancer, head and neck squamous cell carcinoma (HNSCC), diffuse large B-cell lymphoma (DLBCL), microsatellite stable colorectal cancer (MSS CRC), triple negative breast cancer (TNBC), cutaneous melanoma and metastatic castration resistant prostate cancer (mCRPC) will be enrolled. All patients must have disease amenable to biopsy and must be willing to undergo biopsy at screening/baseline, and during the course of study treatment as per protocol requirement. For Parts 1 and 2, patients must not have received prior immunotherapy (with the exception of the following IO pretreated groups: cutaneous melanoma, HNSCC and RCC). Prior immunotherapy status for Part 3 will depend on the tumor groups selected and their standard of care treatments at the time. As of protocol amendment 6, Part 3 will be opened to further assess TNBC patients with a PD-L1 SP-142 IC score of 0 (<1%). A second tumor group will be considered for Part 3 after completion of Part 1.Japanese safety run-in part can enroll any tumor type included in Parts 1,2 and 3.
Inclusion criteria	• Male or female patients ≥18 years of age. 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. • Histologically documented advanced or metastatic solid tumors or lymphomas • Part 1: histologically confirmed renal cell carcinoma (RCC), pancreatic cancer, urothelial cancer, head and neck squamous cell carcinoma (HNSCC), diffuse large B-cell lymphoma (DLBCL), microsatellite stable colorectal cancer (MSS CRC), triple negative breast cancer (TNBC), cutaneous melanoma or mCRPC • Patients with colorectal cancer must have microsatellite stable (MSS) disease as detected by PCR-based assay or mismatch repair proficient as detected by immunohistochemistry and confirmed RAS status (KRAS and NRAS) by standard testing of tumor specimen based on local available laboratory data. • Patients with unresectable or metastatic cutaneous melanoma must have confirmed BRAF V600E status by standard testing of tumor specimen, based on local available laboratory data. • Part 2: histologically confirmed diagnosis of advanced/metastatic NSCLC. For those with mixed histology, there must be a predominant histology • Patients should have confirmed EGFR and ALK status when clinically indicated and performed per standard testing of tumor specimen based on local available laboratory data. • Part 3: histologically confirmed diagnosis of selected advanced/metastatic malignancies. Based on emerging data from Part 1, Part 2 and latest scientific literature along with discussion between Novartis and study investigators, one or two tumor groups will be further explored in Part 3. As of protocol amendment 6, Part 3 will be opened to further assess TNBC patients with a PD-L1 SP-142 IC score of 0 (<1%). A second tumor group will be considered for Part 3 after completion of Part 1. • Safety run-in part in Japanese patients can enroll any tumor type included in Parts 1 2, and 3. • Patient (except for those participating in Japanese safety run-in) 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 screening, and again during therapy on this study. The use of recent sample is permitted under the following conditions (both must be met):

	• Biopsy was collected ≤ 6 months before 1st dose of study treatment and available at the site. • No antineoplastic therapy was given to the patient since collection of biopsy (with the exception of IO pretreated cutaneous melanoma, HNSCC and RCC). • Part 1 – 3 only: Patients (other than those with DLBCL) must previously have received at least 1 and no more than 3 prior lines of therapy (with the exception of IO pretreated cutaneous melanoma, HNSCC and RCC) for their disease, specifically including the following, unless considered inappropriate for the patient (e.g. safety concern, label contraindication): • MSS CRC: • Patients with MSS colorectal cancer must have received (or be intolerant to) prior therapy with fluoropyrimidine-oxaliplatin- and irinotecan- based regimens. • Patient with wild type RAS must have received prior treatment with an antibody targeting EGFR (e.g. cetuximab or panitumumab) • TNBC: • Part 1: Patients with triple negative breast cancer must have received a prior taxane containing regimen. • Part 3: • Patients should have documented disease progression following, or intolerance to, no more than 2 prior lines of chemotherapy for advanced or metastatic disease. Neoadjuvant and/or adjuvant chemotherapy administered with curative intent will count as one prior line of therapy, if disease recurred within 12 months of the last treatment. • Patients must have received prior systemic treatment that included taxane-based chemotherapy for (neo) adjuvant or metastatic disease. • Patients should have a known PD-L1 status as per local available testing determined by VENTANA PD-L1 SP142 Assay with IC score of 0 (<1%) • Urothelial Cancer: • Patients with urothelial cancer must have received a prior platinum-containing regimen or be ineligible for cisplatin. • RCC: • IO naive RCC: Patients with renal cell carcinoma must have received a prior VEGF tyrosine kinase inhibitor (TKI). • IO pretreated RCC: Patients with RCC with no more than 2 prior lines of therapy. Patient must have received a prior VEGF TKI and have been pretreated with an anti-PD-1/PD-L1 as a single agent or in combinations • HNSCC: • IO Naive HNSCC: Patients with squamous cell carcinoma of head and neck (HNSCC) with no more than 3 prior lines of therapy. Patient must have received a prior platinum-containing regimen and have not been previously treated with any anti-PD1/L1 agents in single agent/combinations. • IO pre-treated HNSCC: Patients with HNSCC with no more than 2 prior lines of therapy. Patient must have received a prior platinum-containing regimen and have been pretreated with an anti-PD-1/PD-L1 as a single agent or in combinations • Cutaneous Melanoma: • Patients must previously have received at least 1 and no more than 2 prior lines of therapy.

[redacted]

	• BRAF V600E wild type patients: must have received anti-PD-1/PD-L1 single-agent, or in combination with anti-CTLA-4 therapy • BRAF V600E mutant patients: must have received prior anti-PD-1/PD-L1 single-agent, or in combination with anti-CTLA-4 therapy. In addition, subjects must have received prior BRAF V600E inhibitor therapy, either single-agent or in combination with a MEK inhibitor • Metastatic castration resistant prostate cancer (mCRPC): • Of the 1-3 prior lines of therapy that the patient has received, patients must have received and failed at least one line of treatment after emergence of castration resistant disease • DLBCL: • Patients with DLBCL should be limited to those with no available therapies of proven clinical benefit. • Patient should have had prior autologous hematopoietic stem cell transplantation (auto-HSCT) or determined to be ineligible for auto-HSCT. • NSCLC: • Patients with NSCLC must have received a prior platinum-based combination. • For patients with NSCLC, EGFR mutation with exon 19 deletion or L858R mutation (Exon 21) or anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangement positive must have failed prior Tyrosine-kinase inhibitor (TKI) therapy. • Patients with EGFR positive NSCLC with a T790M mutation must have progressed on osimertinib or discontinued due to toxicity • Patients should have had prior autologous hematopoietic stem cell transplantation (auto-HSCT) or determined to be ineligible for auto-HSCT. • Patients must not have received prior immunotherapy (previous immune checkpoint inhibitors; single agent and/or combination therapy with anti-CTLA-4, anti-PD-1, anti-PD-L1), with the exception of groups: IO pretreated cutaneous melanoma, HNSCC and RCC in Part 1, NSCLC patients enrolled in Part 3 and Japanese safety run-in part. • Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as >20 mm with conventional techniques or as >10 mm with spiral computer tomography (CT) scan, Magnetic Resonance Imaging (MRI), or calipers by clinical exam.
Exclusion criteria	• Ongoing or prior treatment with A2aR inhibitors. Patients previously treated with A2aR inhibitors for non-oncologic indications (e.g. Parkinson's disease) may be considered for enrollment on a case by case basis. • 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, 6 weeks is indicated as washout period. For patients receiving anticancer immunotherapies, 4 weeks is indicated as the washout period. Gonadotropin-releasing hormone (GnRH) therapy to maintain effective testosterone suppression levels is allowed for mCRPC patients. • Current or prior use of immunosuppressive medication within 28 days before the first dose of PDR001, with the exception of intranasal/inhaled corticosteroids or systemic corticosteroids at physiological doses (not exceeding equivalent of 10 mg/day of prednisone) • History of interstitial lung disease or non-infectious pneumonitis • History of another primary malignancy except for: • Malignancy treated with curative intent and with no known active disease ≥2 years before the first dose of study drug and of low potential risk for recurrence

[redacted]

	• Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease • Adequately treated carcinoma in situ without evidence of disease • Active or prior documented autoimmune disease within the past 2 years. Patients with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded. • More than 2 or 3 prior lines of therapy (as indicated above for each tumor group), except for Japanese safety run-in part.
Investigational and reference therapy	NIR178 and PRD001 administered as a combination
Efficacy assessments	Tumor response according to RECIST Version 1.1 and iRECIST (for solid tumors), or Cheson et al (2014) (for lymphoma) assessed by investigator. For mCRPC, tumor assessments will also include the recommendations from the PCWG3. To characterize changes in the immune infiltrate in tumors
Safety assessments	Frequency, severity and seriousness of AEs, laboratory abnormalities and other safety parameters. Dose interruptions, reductions and dose intensity.
Other assessments	[redacted]
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. Data will be summarized using descriptive statistics (continuous data) and/or contingency table (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements and all relevant PK and PD measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.
Key words	Immunotherapy, A2aR, PDR001, NIR178, NSCLC, solid tumors

[redacted]

1 Background

The immune system is a critical regulator of tumor biology with the capacity to support or inhibit tumor development, growth, invasion and metastasis. However, over time and under pressure from immune attacks, tumors have developed strategies to successfully evade the host immune system. Various molecular and cellular mechanisms responsible for tumor evasion have been identified. Strategies designed to harness the immune system (immunotherapy) are the focus of several recent promising therapeutic approaches for cancer patients. Immunotherapy has demonstrated impressive outcomes for some patients with cancer (Ohta et al 2006, Pardoll 2012, Sitkovsky et al 2014, Zarek et al 2008). The success of checkpoint blockade in recent clinical trials has been a major step forward in the development of immunotherapy for the treatment of cancer, confirming the clinical importance of tumor immune evasion through usurping fundamental pathways of immune regulation.

In March 2015, nivolumab was approved by the Food and Drug Administration (FDA) for the treatment of metastatic squamous non-small cell lung cancer (NSCLC) that has failed chemotherapy, based on results of the pivotal phase III CheckMate-017 trial (Brahmer et al 2015), which showed improved overall survival (OS) compared to docetaxel in NSCLC patients with squamous cell histology (9.2 vs 6.0 months; HR = 0.59; 95% CI, 0.44-0.79; P = 0.00025). More recently, the phase III CheckMate-057 trial met the primary endpoint of improved OS (meetinglibrary.asco.org).

With the success of cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) inhibition in clinical trials, significant effort has focused on uncovering other targetable checkpoint pathways active in the tumor microenvironment. In this regard, adenosine signaling through the A2a receptor has been found to function as one such promising negative feedback loop.

Like CTLA-4, PD-1 and PD-L1, adenosine signaling in the inflammatory setting serves to dampen immunologic response and protect tissues from associated injury. While extracellular adenosine levels are typically very low, tissue breakdown and hypoxia (common to inflammatory and tumor microenvironments) generate high levels of extracellular adenosine (Dubyak et al 1993, Blay et al 1997). Extracellular adenosine can signal through a set of four G-protein-coupled receptors: A1, A2a, A2b, and A3 (Robeva et al 1996). Adenosine signaling through A2a and A2b receptors expressed on a variety of immune cell subsets and endothelial cells has been established as having an important role in protecting tissues during inflammatory responses (Zarek et al 2007, Fishman et al 2009, Young et al 2014). Because of its distribution and dynamic expression pattern on a broader array of immune cells, most of this protective effect is thought to be secondary to signaling through the high-affinity A2a adenosine receptor. A2a receptor blockade represents the potential next generation of immune checkpoint inhibition in cancer immunotherapy.

[redacted]

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Adenosine A2a Receptor (A2aR) overview

Adenosine in the tumor microenvironment inhibits T cells. Adenosine is a potential mediator of immunotherapy resistance based on the knowledge that the extracellular tumor microenvironment contains high levels of adenosine as a consequence of anaerobic glycolysis in hypoxic regions; preferential utilization of aerobic glycolysis for energy metabolism in non-hypoxic regions (the Warburg effect); and tumor cell expression of the ectonucleotidase CD73 that catabolizes Adenosine monophosphate (AMP) to produce adenosine. It had been known that adenosine produced within the hypoxic microenvironment of inflamed tissue functions to limit the exuberance of the inflammatory response to reduce collateral damage of normal tissue by inflammatory cells and cytokines. This is due to a direct inhibitory effect on T cells that express A2aRs52, leading to discovery that adenosine in the tumor microenvironment interferes with anti-tumor immunity.

Expression of A2a adenosine receptor (A2aR) has been reported on monocytes/macrophages, mast cells, granulocytes, lymphocytes, Dendritic cell (DC), natural killer (NK) cells, endothelial cells, and airway epithelial cells (Ahmad et al 2009, Fredholm 2007). Nutrient deprivation and accumulation of metabolites in the tumor microenvironment (TME) like adenosine have been identified as a new regulatory node to target to re-establish anti-tumor immunity. Of the four known types of adenosine receptors, A2aR is the predominantly expressed subtype in most immune cells (Antonioli et al 2013, Fredholm et al 2001, Sitkovsky and Ohta 2013) Beyond the induction of regulator T cell (Treg) with stronger immunosuppressive phenotype (Ohta et al 2012), the stimulation of A2aR results in inhibition of proliferation, cytokine production and cytotoxicity of T cells and NK cells as well as decreased antigen presentation by macrophages/dendritic cells (Antonioli et al 2013, Fredhold et al 2001, Sitkovsky and Ohta 2013) (Figure 1-1). The combination of an adenosine antagonist (SCH58261 or ZM241365) with T cell checkpoint blockade (an anti-PD1 or anti-CTLA4 agent) resulted in a reduction of metastasis in the B16F10 melanoma model (Mittal et al 2014, Iannone et al 2014). This finding supports the non-redundant role for adenosine and checkpoints molecules in the immune response in cancer and provides a rationale for testing this combination in the clinic.

In vivo studies using mice with global knockout of A2aR have demonstrated enhanced rejection of highly immunogenic tumors including melanoma and lymphoma in a CD8 T cell dependent manner (Ohta et al 2006, Waickman et al 2012). However, in these same mice models, global deletion of A2aR did not impact growth rates of other immunogenic tumors including B16F10 melanoma and MB49 bladder carcinomas (Ohta et al 2006). Others have reported shortened survival of infiltrating T cells and impaired anti-tumor immunity with both global, and lymphoid specific genetic depletion of A2aR (Cekic et al 2013). A genetically modified strain of C57Bl6 mice engineered to have A2aR depleted only in lymphoid cells displayed enhanced growth rates of ectopically implanted B16F10 melanoma and MB49 bladder tumors, reduced effector-memory differentiation, and reduced expression of anti-apoptotic IL7Ra in memory T cells (Cekic and Linden 2014). Together, these data show that while A2aR deletion leads to robust immune activation in vivo, global and persistent A2aR deletion can have deleterious effects on anti-tumor immunity and promote tumor growth in some in vivo models.

[redacted]

Therefore, pharmacologic inhibition of A2aR in the clinic may require careful exploration of both continuous and intermittent inhibition in order to optimize both the intensity and duration of A2aR blockade to achieve maximal anti-tumor effect (Figure 1-1).

Figure 1-1 Adenosine A2a Receptor (A2aR) signaling

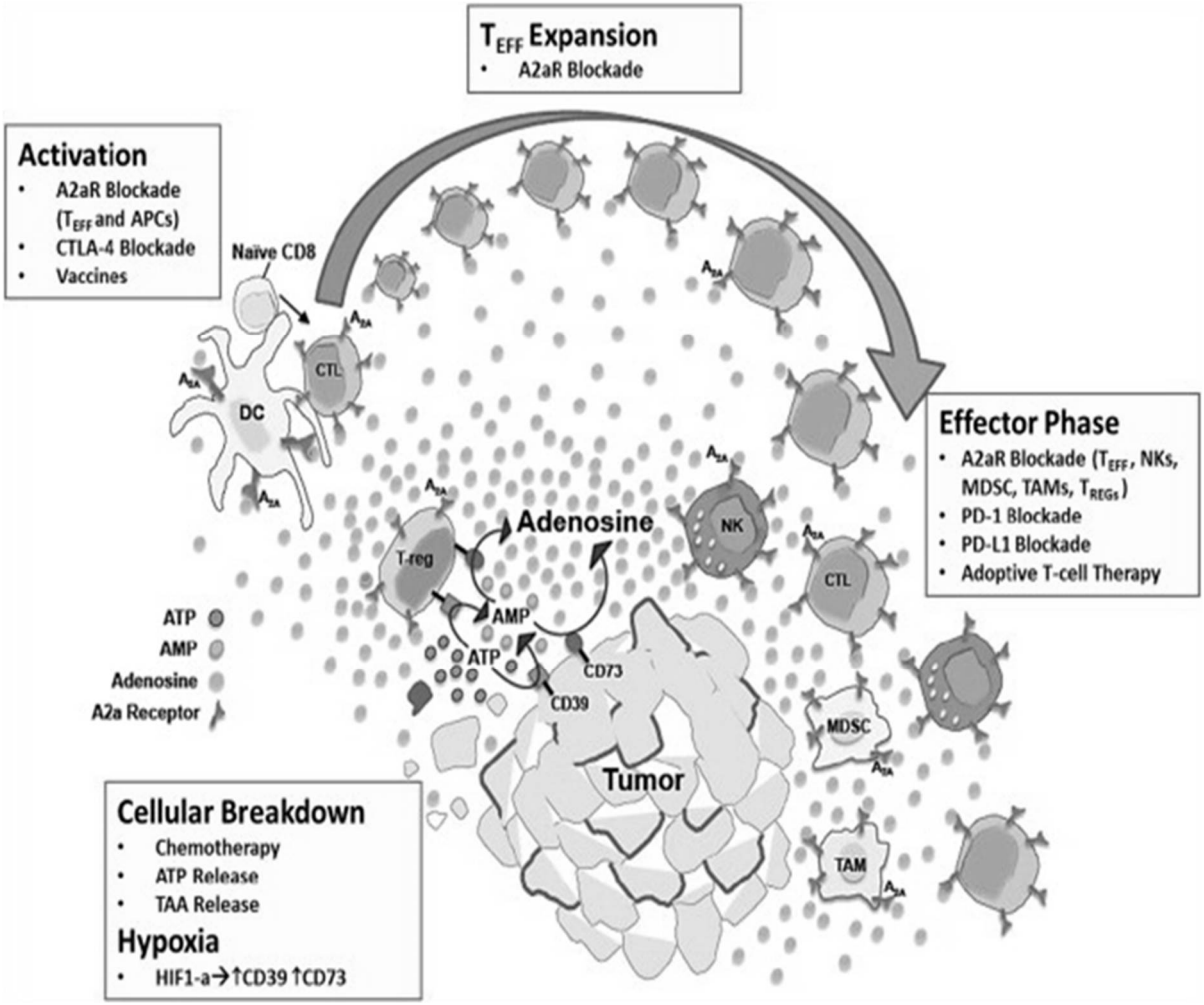


Figure adapted from Leone et al (2015).

1.1.2 PD-1 overview

PD-1 is a critical checkpoint receptor that is expressed by effector T cells (Teffs) upon activation (Okazaki et al 2013). It is also expressed by B cells, NK T cells, CD4+ Treg cells, and some DC subsets upon activation (Francisco et al 2010). Its ligands, PD-L1 and programmed death-ligand 2 (PD-L2) are expressed by dendritic cells, macrophages and monocytes, and can be induced on virus-infected cells and many types of tumors (Keir et al 2008). Engagement of PD-1 with its ligands PD-L1 and PD-L2 negatively regulates effector T cell signaling and function and protects the tumor cells from the induction of apoptosis by Teffs.

[redacted]

The PD-1/PD-L1 axis is exploited by many tumor types to avoid detection by the adaptive immune system (Murphy 2011). Blockade of the PD-1 pathway has been shown to lead to increased numbers of Teffs through induction or expansion and improved cytolytic activity towards tumors. Additionally, PD-1 blockade is associated with accumulation of Teffs and a reduced numbers of Tregs at the tumor site (Wang et al 2009, Mangsbo et al 2010, Mkrtichyan et al 2011, Rosenblatt et al 2011).

Both preclinical and clinical studies have demonstrated that anti-PD-1 blockade restores activity of "exhausted" Teffs and results in robust anti-tumor response. Clinical data with other anti-PD-1 antibodies have demonstrated that PD-1 checkpoint inhibition results in clinically relevant anti-tumor activity in a variety of solid tumors, including melanoma, NSCLC, renal cell carcinoma (RCC) and head and neck squamous cell carcinoma (HNSCC) with an acceptable and manageable safety profile (Topalian et al 2012, Hamid et al 2013, Lyford-Pike et al 2013, Powles et al 2014, Topalian et al 2014, Ansell et al 2015, Homet Moreno and Ribas 2015, Michel Ortega and Drabkin 2015, Sunshine and Taube 2015).

Despite these successes, many patients do not respond to/or relapse following treatment with PD1 inhibitors. Additional strategies employing combination of PD-1 inhibition with other immune checkpoints are hypothesized to improve the response rates seen with PD-1 inhibitors alone. Combined inhibition of the PD-1 pathway and A2aR has been shown to enhance CD8 T and NK cell anti-tumor activity and reduce metastatic burden in preclinical models (Young et al 2014, Waickman et al 2012), supporting evaluation of this combination in the clinic.

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

1.2.1 Overview of NIR178

NIR178 [5-*bromo-2,6-di(1H-pyrazol-1-yl)pyrimidin-4-amine*], a new, non-xanthine-based compound, is a potent oral adenosine A2a receptor antagonist being developed by Novartis. NIR178 has been profiled in binding assays against the four known adenosine receptors demonstrating selectivity for A2A compared to the other adenosine receptors (A1, A2b, and A3). The inhibition constants (Ki) were 12nM against A2A and over 1uM for the other adenosine receptors. Furthermore, the compound was able to inhibit the increase of cyclic adenosine monophosphate (cAMP) induced by an adenosine A2A agonist with a Ki of 25nM.

As NIR178 was in-licensed by Novartis from Palobiofarma, pre-clinical and clinical data generated with this compound prior to this study and detailed in the Investigator's Brochure (IB) uses the Palobiofarma designation, PBF-509. For further information, please refer to the [NIR178 (PBF-509) Investigator's Brochure].

1.2.1.1 Non-clinical experience

Initial evaluation of the anti-tumor activity of NIR178 was done with ex vivo experiments using lung cancer cells from patient biopsies and in vivo experiments in syngeneic mice using B16-CD73+ and MCA205 cells. The ex vivo experiments studied the effect of NIR178 on the secretion of interferon gamma (IFNγ) in tumor cells and tumor infiltrating lymphocytes (TIL) arising from treatment resistant tumors from patients with lung cancer. NIR178 alone was able

[redacted]

to increase secretion of IFNγ in tumors enriched with TIL of patient donors. In four out of six human lung tumors assayed, NIR178 (1µM) was able to stimulate the secretion of IFNγ and some other interleukins into the medium, demonstrating robust immune stimulation of the infiltrating lymphocytes present within the tumors.

The combination of NIR178 (1µM) with either an anti PD-L1 or an anti-PD1 antibody appears to increase interferon gamma secretion of those tumors synergistically. The synergism of anti-PD1 antibody and NIR178 has been assessed in MC38 syngeneic tumor models. Of note, the anti-PD1 antibody used in this experiment was not PDR001 (which is not mouse cross-reactive) but a surrogate antibody (clone 5D1).

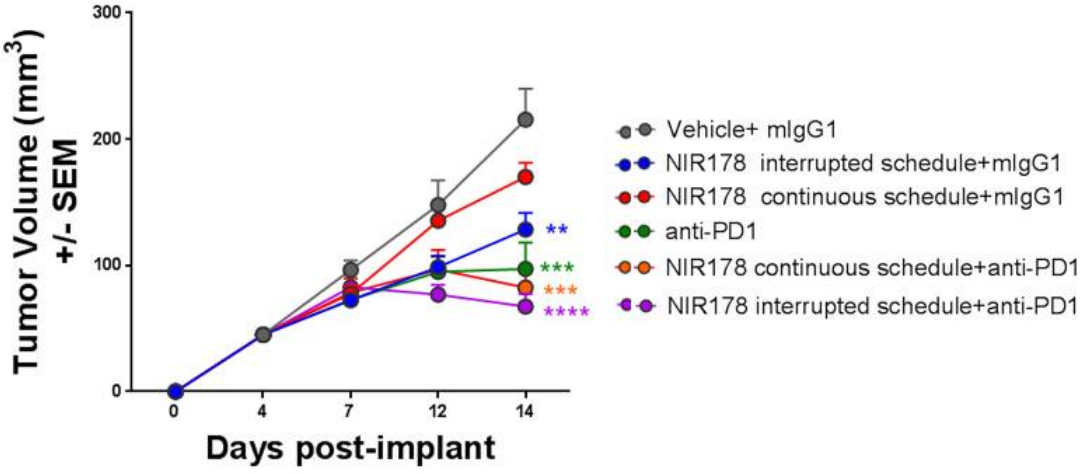
In order to understand whether different schedules of administration of NIR178 could affect the outcome of the combination, continuous and intermittent schedules of NIR178 in the presence or absence of anti-PD1 antibody were compared.

A cohort of 90 C57Bl/6 mice were subcutaneously implanted with 1 x 10^6 MC38 cells and randomized at day 5 when tumors were palpable. Tumor bearing mice were distributed in six groups of treatment as described below:

1. Vehicle control (0.5% SLS; 0.5% MC)
2. NIR178 50 mg/kg BID, continuous schedule
3. NIR178 50 mg/kg BID, for 4 consecutive days followed by 3 days off
4. Anti-PD1 (10mg/kg) once a week + vehicle
5. NIR178 50 mg/kg BID, continuous schedule + anti-PD1 once a week
6. NIR178 50 mg/kg BID for 4 consecutive days followed by 3 days off + anti-PD1 (10 mg/kg)

Mice were treated for 9 days with vehicle control or PBF-509 alone or together with anti- PD1 antibody at the above indicated doses and schedules by oral gavage from day 5. Tumor volume was measured twice a week as illustrated in Figure 1-2. P values were calculated using Mann-Whitney test.

Figure 1-2 Effect of NIR178 chronic treatment in the MC38 syngeneic mouse model



[redacted]

Intermittent dosing of NIR178 demonstrated a trend towards better control of tumor growth than chronic continuous dosing schedules in mice (Figure 1-2). Furthermore it was observed that the statistical significance of the response of the combination group (NIR178 and anti-PD1) was stronger when three days of drug holiday was introduced into the dosing schedule. These subtle, but statistically significant differences in tumor growth rates between continuous and intermittent schedules lend support to further exploring intermittent scheduling of NIR178 in the clinical setting.

1.2.1.2 Non-clinical pharmacokinetics and drug metabolism for NIR178

The non-clinical pharmacokinetics of NIR178 has been investigated in mouse, rat, and dog *in vivo* models. The clearance and volume of distribution determined for NIR178 were high in both the rat and the dog. The apparent half-life was short to moderate in rat and dog. NIR178 was orally available in mouse, rat, and dog with the bioavailability in rat determined to be moderate (~44%).

In vitro plasma protein binding assessment of NIR178 showed low to moderate protein binding (low, 0-50% bound; moderate 50-90% bound) across species.

Hydroxylation and subsequent glucuronidation, sulfonation, or pyrazole ring-opening were the metabolic pathways observed in incubates of NIR178 with rat, dog, and human cryopreserved hepatocytes. None of the NIR178 metabolites characterized were determined to be unique to human. A hydroxylated metabolite of NIR178 named NJI765 (M1 or PBF-849) was observed circulating in both rat and dog from toxicology studies at exposures less than the parent exposure. The cytochrome P450 (CYP) enzyme 1A2 was found to be the primary enzyme responsible for the clearance of NIR178 in human liver microsomes.

NIR178 was determined *in vitro* to be a potent reversible inhibitor of human (h) CYP1A2 and a weak inhibitor of hCYP2D6 and hCYP2C19. Based on a mechanistic static model of drug-drug interactions (DDIs), NIR178 has the potential to cause increased exposures for hCYP1A2 substrates.

Results from *in vitro* luciferase assays demonstrate that NIR178 is unable to activate Pregnane X Receptor (PxR) and aryl hydrocarbon receptor (AhR), suggesting that NIR178 is not likely to be an inducer of drug metabolizing enzymes.

NIR178 was tested as an inhibitor of the human organic anion-transporting polypeptide (OATP) proteins 1B1 and 1B3 using *in vitro* cell lines expressing OATP1B1 and OATP1B3. NIR178 inhibited the transport activity of OATP1B1 with a maximum observed inhibition of 33% at 50 μM, and had no effect on OATP1B3 activity.

NIR178 was tested in *in vitro* cell lines as an efflux inhibitor of the human breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp). NIR178 showed no inhibition of a P-gp human ortholog. NIR178 maximally inhibited BCRP *in vitro* by 73.9% at 50 μM with an estimated IC50 of 14.2 μM. NIR178 may cause an increase in the systemic exposure of co-medications whose clearance is significantly mediated by BCRP, but not P-gp, provided that sufficiently high concentrations of NIR178 are achieved *in vivo*.

Please refer to [NIR178 (PBF-509) Investigator's Brochure] for further details.

[redacted]

1.2.1.3 Biopharmaceutics

A crossover relative bioavailability study [Study DMPK R1701376] in Beagle dog was conducted to screen the *in vivo* pharmacokinetic performance of a film-coated tablet (FCT) formulation prototype of NIR178 in comparison to the existing hard gelatin capsule (HGC) formulation used in current clinical trials. In this study, both formulations were administered as intact dosage form and as a suspension in water. When administered orally at a dose of 80 mg as intact dosage forms, the average bioavailability of NIR178 in FCT increased by 17% compared to the HGC. However, when both formulations were administered after making a suspension in water, the average bioavailability of NIR178 in FCT increased by 44% compared to the HGC existing formulation. The study also seems to suggest less variability in PK of NIR178 with the FCT formulation (Table 1-1).

Data from this dog PK study guided the selection of the proposed film-coated tablet which will be introduced in the current clinical study. The proposed film-coated tablet led to reduced variation in PK and improved bioavailability of NIR178.

Table 1-1 Relative bioavailability of a film-coated tablet (FCT) formulation variant of NIR178 compared to the existing capsule formulation (hard gelatin capsule) in Beagle dog

Dosage form	Dose	Median Tmax (hr)	Mean C_{max}, ng/mL (CV%)	Mean AUC_{last}, ng*hr/mL (CV%)	AUC_{last} fold change vs. reference
Hard gelatin capsule (intact) [reference]	80 mg PO	1.0	3,410 (69)	6,940 (69)	
Film-coated tablet (intact)	80 mg PO	2.0	4,770 (34)	8,110 (41)	1.17
Hard gelatin capsule (suspension[1]) [reference]	80 mg PO (Suspension in water)	1.0	6,090 (53)	10,000 (64)	
Film-coated tablet (suspension[1])	80 mg PO (Suspension in water)	1.0	7,880 (25)	14,400 (25)	1.44

Source: Study DMPK R1701376

Study used a crossover design with N=6 dogs per dosing period;

[1]50 mL water was used to bring the capsule or tablet drug product to a suspension prior to oral administration via gavage.

Abbreviations: PO, orally; C_{max}, maximum observed plasma concentration; AUC_{last}, area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration.

[...]

1.2.1.4 Clinical experience

Two healthy volunteer studies were conducted with single agent NIR178 and there is one ongoing Phase I/Ib trial (CNIR178X2103J) of NIR178 as single agent and in combination with PDR001 in patients with advanced non-small cell lung cancer (NSCLC).

[redacted]

In the first in human trial in healthy volunteers conducted by Palobiofarma (using compound designation PBF-509), seven single ascending doses (10 mg, 20 mg, 40 mg, 80 mg, 160 mg, 320 mg, and 480 mg) were evaluated. NIR178 was found to be safe and well tolerated with no dose-limiting toxicity (DLT) reported at all administered dose levels. No clinically relevant changes related with the NIR178 administration were found in the safety parameters evaluated (ECG, vital signs, blood chemistry, and hematology) in any of the healthy volunteers participating in the study.

In a subsequent multiple ascending dose clinical trial, the safety, tolerability of two doses (80 and 160 mg) of NIR178 were evaluated administering the compound once daily for 8 days. Similar to the single dose administration trial, NIR178 was found to be safe and well tolerated at both doses tested with no DLTs reported.

CNIR178X2103J is an ongoing phase I/Ib study evaluating the safety, tolerability, and anti-tumor activity of NIR178 as single agent and in combination with PDR001 in patients with advanced/metastatic NSCLC. The study design utilizes a modified 3+3 dose escalation algorithm.

Dosing began on 15 October, 2015 with PBF-509 (NIR178) given orally twice daily in 28 day cycles. As of January 15, 2020, the single agent NIR178 dose escalation part has enrolled 25 patients across five dose levels: 80mg BID (n=3), 160mg BID (n=3), 320mg BID (n=7), 480mg BID (n=6) and 640mg (n=6). In general, NIR178 has been well tolerated as single agent and 24 out of 25 patients (96%) have discontinued treatment. Two patients died on treatment due to underlying disease. There were two DLTs reported: Grade 3 nausea and Grade 3 ALT/AST increased, both at the 640mg dose level. The maximum tolerated dose of oral single agent of NIR178 was declared at 480mg BID. No grade 4 adverse events were reported. Four patients out of 25 experienced grade 3 treatment related toxicity which include nausea, pneumonitis, AST/ALT increase and lipase increase. Among 19 evaluable patients (out of 25 dosed on single agent NIR178), best overall responses include 1 patient with complete response (CR), 1 patient with partial response (PR) and 7 patients with stable disease (SD). The maximum tolerated dose (MTD) for single agent NIR178 was declared as NIR178 480 mg BID (Chiappori et al 2018).

The combination of NIR178 with PDR001 has been evaluated in the phase I/Ib study CNIR178X2103J as a parallel dose escalation in patients with advanced NSCLC. Dose escalation followed a modified 3+3 algorithm, in which PDR001 was dosed at the RDE of 400mg IV Q28 days and NIR178 was escalated from a starting dose of 160mg BID. Dosing with the combination began on August 11, 2016. As of January 15, 2020, 25 patients have been treated with NIR178 in combination with PDR001. There were four dose-limiting toxicities reported: 2 patients with grade 3 pneumonitis, one patient with grade 3 fatigue and one patient with grade 3 ALT/AST increase. The most frequent (≥10%) drug-related AEs were nausea (24%), AST/ALT increase (both 20%), fatigue (16%), and lipase increase (12%). The most frequent (≥5%) Gr 3 drug-related AEs were AST increase (12%), ALT increase, lipase increase and pneumonitis (all 8%). At the time of data cutoff, there was 1 complete response (CR) and 1 partial response (PR) and 12 stable disease (SD) reported. The MTD for NIR178 in combination with PDR001 400 mg Q4W was declared as 240 mg BID (Chiappori et al 2018). Please refer to [NIR178 (PBF-509) Investigator's Brochure] for further details.

[redacted]

In the ongoing CNIR178X2201 trial, as of August 3, 2020, 13 patients were treated with the NIR178 240mg dose in combination with PDR001 400mg Q4W with available safety data. The first 10 patients enrolled at the NIR178 240mg dose, have completed at least one cycle of treatment with G3 AEs suspected to be related to study drug occurring in two patients. Less than 33% of the first 10 patients enrolled in this regimen experienced a G3/G4 AE suspected to be related to study drug, which is below the defined threshold as outlined in Section 6.2.3. To date, the dose of NIR178 240mg BID in combination with PDR001 400mg Q4W has shown to be safe and well tolerated.

1.2.1.4.1 Clinical pharmacokinetics of NIR178

The pharmacokinetics of NIR178 both single and repeat dose of NIR178 has been characterized in healthy volunteers in prior studies as well as in NSCLC patients in an ongoing Phase I/Ib study (CNIR178X2103J). A mono-oxygenated metabolite (NJI765) was also monitored in healthy volunteer studies. In healthy volunteers, (single ascending dose levels of 10, 20, 40, 80, 160, 320 and 480 mg) NIR178 demonstrated rapid absorption and elimination with a Tmax of 0.17-4 hrs and a terminal elimination half-life of 1.06-3.83 hrs. Concentrations in the systemic circulation were generally below the lower limit of detection at 10 and 20 mg. Systemic exposure (Cmax and AUC) over the dose range of 40 to 480 mg generally increased more than proportionally with dose; inter-subject variability was moderate to high.

In the Phase I/Ib study in advanced NSCLC, patients were dosed NIR178 orally twice daily (BID) as a single agent 80, 160, 320, 480, and 640mg. NIR178 was rapidly absorbed with a median Tmax occurring at 2 hours post-dose. NIR178 featured nonlinear pharmacokinetics, both dose- and time-dependent. Similarly to healthy volunteers, NIR178 systemic exposure increased more than proportionally with dose following single and repeated BID dosing of 80 to 640 mg. Despite of its short terminal half-life, the accumulation ratio of NIR178 was approximately 3-fold after one week of multiple daily dosing compared to a single dose. Inter-subject variability in Cmax and AUC was moderate to high. The pharmacokinetics of NIR178 (160, 240, and 320 mg BID) when given in combination with PDR001 (400 mg every 4 weeks) in patients with advanced NSCLC is largely similar to that of NIR178 alone, suggesting no clinically relevant interaction between the two drugs.

Please refer to the [NIR178 (PBF-509) Investigator's Brochure] for further details.

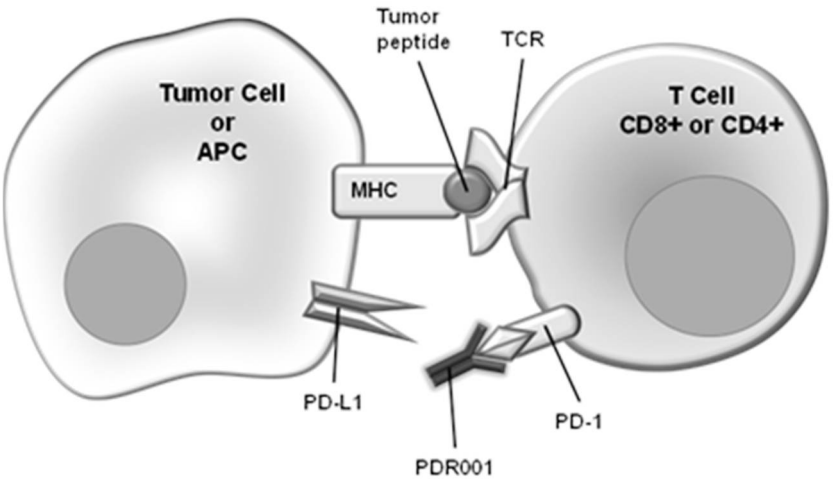
1.2.2 Overview of PDR001

PDR001 is a high-affinity, ligand-blocking, humanized anti-programmed death-1 (PD-1) IgG4 antibody that blocks the binding of Programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (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].

[redacted]

Figure 1-3 Blockade of PD-1/PD-L1 interaction by PDR001



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

1.2.2.1 Non-clinical experience

PDR001 binds specifically and with high affinity to human PD-1. In Biacore assays, the constant of dissociation of PDR001 on human PD-1 is 0.827 nM. In lymphocyte stimulation assays using human blood ex vivo, PDR001 enhances interleukin-2 (IL-2) production by approximately 2 fold in response to super antigen stimulation with Staphylococcal enterotoxin B. 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.

The non-clinical toxicology of PDR001 was evaluated in a five week good laboratory practice toxicology study in cynomolgus monkeys with safety pharmacology endpoints and an eight week recovery. Doses as high as 100 mg/kg/week were evaluated without drug-related in-life, mortality, organ weight changes, or macroscopic findings noted. At the highest doses tested, macrophage infiltrates in the spleen and limited mononuclear infiltrates in the vascular and perivascular space were noted.

For further details, please refer to the [PDR001 Investigator's Brochure].

1.2.2.2 Clinical experience

The first in human phase I/II study CPDR001X2101 started enrollment on 27 April 2015 and is ongoing in patients with advanced malignancies. The dose escalation part of the study was completed with a total of 58 patients treated at the dose levels of 1, 3 and 10 mg/kg every two weeks (Q2W) and 3 and 5 mg/kg every 4 weeks (Q4W). No patient experienced a DLT. The pharmacokinetics (PK) analysis of the dose escalation data using a population approach and the expected wide therapeutic index of PD-1 inhibitors support the use of flat dosing for PDR001 of 400 mg Q4W or 300 mg Q3W. The expected PDR001 Ctrough concentrations using either dosing regimen exceed the EC50 for PD-1 blockade by approximately 75-fold in an ex vivo assay in peripheral blood mononuclear cells (PBMCs). Based on the available PK and

safety data, the recommended phase II doses (RP2D) of PDR001 has been declared as 400 mg i.v. Q4W or 300 mg i.v. Q3W for combination treatment regimens for which this may be more convenient.

PDR001 is currently being studied alone or in combination with other agents in ongoing phase I/Ib/II clinical trials. The preliminary toxicity profile appears to be similar to that of marketed inhibitors of PD-1 including the type, severity and frequency of occurrence of immune-mediated adverse events. As observed with other PD-1 inhibitors, immune-mediated toxicities observed with PDR001 are reversible in many cases. In some cases, they may require treatment with corticosteroids. Certain toxicities are expected to be lifelong and may require replacement therapy with hormones, for example in the case of hypothyroidism. Based on the preliminary data, PDR001 was well tolerated with a safety profile similar to those of other marketed anti-PD-1 antibodies.

For further details, please refer to the [PDR001 Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

The purpose of this phase II study is to evaluate the efficacy and safety of NIR178 in combination with PDR001 in multiple solid tumors and diffuse large B-cell lymphoma (DLBCL) and further explore schedule variations of NIR178 to optimize immune activation through inhibition of A2aR.

Combination therapies using multiple inhibitors of immune function can significantly improve response rates. For example, a nivolumab/ipilimumab combination providing blockade of the PD-1 and CTLA-4 immune checkpoints significantly improved responses for patients with advanced melanoma (Larkin et al 2015). Expanding the depth, breadth and durability of responses to treatment is now an important focus of clinical oncology research. These efforts include targeting different steps in the anti-tumor immune response to stimulate T lymphocyte activity in tumors, reduce suppressive effects of Tregs and myeloid cells, and engender long-lasting immunity through vaccines and enhancers of dendritic cell function (Mellman et al 2011).

The biological mechanisms and the preclinical evidence indicate that adenosine signaling through A2aR is an important immunosuppressive component within the tumor microenvironment, which may limit and possibly mediate resistance to immune checkpoint blockade with PD1 inhibitors. Therefore, pharmacological inhibition of A2aR in combination with PD1 mAb, PDR001, may be an effective way to alleviate immune-suppression, reduce tumor growth, and increase anti-tumor activity of PDR001.

In an ongoing phase Ib dose escalation trial in NSCLC (CNIR178X2103J), NIR178 has demonstrated an overall favorable safety profile as a single agent in dose escalation, with two DLTs observed to date across five dose levels. Early data from dose escalation in combination with PDR001 also shows an overall manageable safety profile. Importantly, encouraging preliminary anti-tumor activity has been observed in a heavily pre-treated NSCLC population (one complete response (CR), one partial response (PR) and twelve stable disease (SD) seen

[redacted]

with single agent NIR178 out of 25 patients treated; 1 CR, 1 PR and 6 SD in combination with PDR001 out of 25 patients treated).

Based on encouraging early clinical activity in NSCLC and tolerability of the combination of NIR178 with PDR001, this phase II study will further explore the efficacy and safety of the combination of NIR178 and PDR001 in multiple tumor types. Intermittent dosing schedules of NIR178 in combination with PDR001 will also be explored in this study as preclinical data shows a trend towards improved control of tumor growth using intermittent dosing of NIR178 in syngeneic mouse models.

For further details, please refer to the [NIR178 (PBF-509) Investigator's Brochure].

2.2 Rationale for the study design

This open label phase II study has three parts: Part 1: Multi-arm Bayesian adaptive signal finding design of NIR178 (dosed continuously) in combination with PDR001 in solid tumors and diffuse large B cell lymphoma (DLBCL); Part 2: Exploration of continuous and intermittent schedules of NIR178 in combination with PDR001 in patients with advanced NSCLC; Part 3: Further evaluation of efficacy of the best performing dosing schedule of NIR178 in combination with PDR001 in one or two tumor groups selected from Parts 1 and 2. The tumor group(s) selected for Part 3 will be based on emerging data from Part 1, Part 2 and latest scientific literature. Parts 1 and 2 will enroll in parallel. As of protocol amendment 6, enrollment in Part 2 has been completed, and the continuous dosing schedule of NIR178 has been selected as the preferred dose regimen as clinical efficacy results do not support the hypothesis that intermittent dosing improves NIR178 + PDR001 antitumor activity. Part 3 will be opened in parallel with Part 1, and will further assess TNBC patients with an IC score of 0 using NIR178 continuous dosing schedule in combination with PDR001. A second tumor group may be considered for Part 3 after completion of Part 1. Additionally, Part 3 will assess the safety and pharmacokinetics of a new FCT formulation of NIR178. The terms tumor types and groups are used interchangeably.

The purpose of Part 1 is to broadly evaluate the efficacy of NIR178 and PDR001 in 11 selected solid tumors and diffuse large B cell lymphoma (DLBCL) using a Bayesian adaptive signal finding design that utilizes predetermined futility/expansion thresholds to best identify tumor types that warrant further study with the combination. Tumor types were selected based on presence of features thought to be associated with adenosine mediated immunosuppression including, but not limited to, gene expression levels of CD73 and A2aR based on data from the Tumor Cell Genome Atlas (TCGA).

In order to effectively screen for efficacy signals across multiple tumor types, a Bayesian adaptive design will be used to identify those tumors in which the combination of NIR178+PDR001 demonstrates superior response rates in relation to that of current standard of care therapies. Based on observed overall response rate (ORR) for the first 10 patients in each tumor type in relation to established historical controls, a Bayesian model employing a hierarchical borrowing algorithm will determine which tumors warrant further expansion to a maximum of 30 patients, using pre-specified futility criteria. The advantages of such Bayesian approaches as opposed to traditional frequentist approaches have been previously described (Berry 2011, Zhen et al 2012). Please see Section 4.1.

[redacted]

The purpose of Part 2 will be to explore the safety, efficacy, [redacted] of continuous and several intermittent dosing schedules of NIR178 in combination with PDR001, in light of preclinical data showing slightly decreased rates of tumor growth in vivo with intermittent dosing schedules of NIR178. In order to control for confounding variables and precisely assess the effect of altering the NIR178 schedule, only patients with advanced NSCLC who are naïve to prior immunotherapy will be enrolled to this part. In order to further balance covariates across the 3 groups, patients will be randomized in a 1:1:1 fashion to one of 3 arms, each evaluating a different dosing schedule of NIR178 within a 28 day cycle. The decision to further explore the intermittent or continuous dosing schedule will be based on the integrated analysis of efficacy, safety [redacted]. Please see Section 4.2.

If Part 2 identifies an intermittent or a continuous dosing schedule of NIR178 in combination with PDR001 as warranting further study, Part 3 will initiate in order to further evaluate the safety and efficacy of the intermittent or continuous NIR178 schedule using a new FCT formulation of NIR178, with two parallel groups of 20 to 30 patients each. One or two tumor groups from Part 1 and/or Part 2 will be further explored in Part 3 with the intermittent or continuous NIR178 schedule based on clinical efficacy [redacted] emerging data. If one of the tumor groups selected for Part 3 is advanced NSCLC, this group will enroll patients previously exposed to checkpoint inhibitors. As of protocol amendment 6, Part 3 will be opened in parallel with Part 1 to further assess the clinical activity in TNBC patients with a PD-L1 SP-142 status of IC=0 using an NIR178 continuous dosing schedule in combination with PDR001. A second tumor group may be considered for Part 3 after completion of Part 1.

Additionally, as per recommendation of the Japanese Health Authority, a safety run-in part will be conducted in Japanese patients dosed at either 80mg or 160mg BID of NIR178 for the first cycle of treatment. The data generated from the safety run-in is considered adequate to evaluate the safety and pharmacokinetic (PK) profiles of single agent NIR178. Since there were no differences in the safety and PK profiles of PDR001 between Japanese and non-Japanese patients treated at the RDE of 400mg IV Q4 weeks in study CPDR001X1101, and given the low likelihood of DDI between NIR178 and PDR001 (Section 2.4.1), following the first cycle safety run-in patients who receive single-agent NIR178 will be treated with the combination of NIR178+PDR001 starting cycle 2 onwards (Section 4.1.4). While the final analysis of safety will use all available safety and pharmacokinetic data (including combination phase with PDR001), the safety of single agent NIR178 in Japanese patients in relation to that of non-Japanese patients treated at the same dose levels in the phase I study CNIR178X2103J, will be the primary determinant of whether or not Japanese patients can join the phase II study. As of Protocol Amendment 6, patients enrolled in the Japanese safety run-in part of the study will be treated with NIR178 240mg hard gelatin capsules BID in combination with PDR001 400mg Q4W starting at Cycle 1 Day 1. Based on the data from the Japanese safety run-in at the 80mg and 160mg, there were no obvious ethnic differences on safety and PK observed between Japanese versus non-Japanese patients. In addition, no DDI has been observed between NIR178 and PDR001. This design also allows Novartis to assess DLT in combination therapy in Japanese patients at the recommended dose.

[redacted]

2.3 Rationale for dose and regimen selection

In this study the selection of dosing regimen is based on the currently available preclinical and clinical safety, efficacy, PK and PK/PD information for the NIR178 and PDR001 combination. Based on currently available data from the ongoing phase 1b study (CNIR178X2103J), NIR178 160mg BID will be administered (continuous or intermittent dosing schedule) in combination with PDR001 at 400 mg every 4 weeks in this phase II study. All newly enrolled patients under Amendment 5 will receive NIR178 240 mg BID in combination with PDR001 400 mg every 4 weeks. Patients enrolled in Part 3 of the study will receive the new FCT formulation of NIR178, starting with a dose of 160 mg BID in combination with PDR001 400 mg every 4 weeks. After the initial 10 patients complete at least the first cycle of treatment, safety and available PK data will be analyzed to determine if an increase of the NIR178 dose to 240 mg BID is warranted, see Section 4.1.3. For the Japanese safety run-in three dose levels of NIR178 will be evaluated (80mg,160mg and 240mg). As of protocol amendment 6, patients enrolled in the Japanese safety run-in will be administered NIR178 240mg hard gelatin capsules BID in combination with PDR001 400mg every 4 weeks starting at Cycle 1 Day 1.

A starting dose of NIR178 160 mg BID in combination with PDR001 using the new FCT formulation was selected based on the following considerations:

- NIR178 240 mg BID in combination with PDR001 400 mg QW4 was declared as MTD, based on clinical data with the existing formulation;
- FCT (administration as intact tablet) increased the bioavailability of NIR178 in dog relative to existing capsule formulation (administered as intact capsule) by 17% (refer to Table 1-1);
- Decrease in variability of PK parameters of FCT (CV% of AUC_{last} decreased from 69 to 41 and CV% of C_{max} decreased from 69 to 34);
- Cumulative safety data of NIR178 at the dose 240 mg BID + PDR001 in other tumor indications (e.g., RCC, mCRPC) using existing capsule formulation is not yet available.

Preliminary evidence, based on emerging data from the current phase 2 study CNIR178X2201, shows that patients may derive more clinical benefit from a higher starting dose of NIR178, more specifically:

- Combined [redacted] pharmacokinetic, and efficacy data show a trend for patients with increases in CD8 T-cell infiltration in on-treatment biopsies to demonstrate greater anti-tumor efficacy. Further, there is evidence of a correlation between exposure, T cell infiltration, and response to provide further support for the higher dose exploration.

[redacted]

- Of the 165 patients (Part I only) treated with NIR178 160mg twice daily continuously in combination with PDR001 400mg every 4 weeks, 99 patients (60.0%) experienced AEs (all grades) suspected to be related to study treatment. The most commonly reported AEs were fatigue (29 patients, 17.6%), increased AST (20 patients, 12.1%), decreased appetite (17 patients, 10.3%), increased ALT (16 patients, 9.7%), nausea (15 patients, 9.1%), vomiting (10 patients, 6.1%), pruritus (9 patients, 5.5%).
  For further details, please refer to the [NIR178 (PBF-509) Investigator's Brochure].
- Exposure-response analysis for safety indicates that the steady-state pharmacokinetic exposure of NIR178 at 240 mg BID combined with PDR001 400 mg Q4W is below the select 33% probability threshold for patients to develop Grade 3-4 AST and/or ALT elevation. Further, preliminary analysis revealed a concentration-dependency in hepatotoxicity AEs across the clinically relevant exposure range of NIR178.
  Despite the positive trend of AST/ALT elevations with exposure, elevation of transaminases was in general reversible and manageable upon dose reduction or interruption based on clinical observation. Therefore, existing guidelines in the protocol for dose reduction and/or interruption for NIR178 are considered to be effective in managing transaminase elevations by decreasing drug exposure (refer to Table 6-2).
- NIR178 240 mg BID + PDR001 400 mg Q4W was determined to be the maximum tolerated dose (MTD) for the double combination and was well tolerated in patients with advanced NSCLC. Increasing the dose of NIR178 to 240 mg BID from 160 mg BID will add one additional dose reduction step if needed, as follows: 240 mg (starting dose), 160 mg (dose level -1, 33% reduction), 120 mg (dose level -2, 25% reduction), and 80 mg (dose level -3, 33% reduction). Dose reduction below 80 mg BID is not allowed (refer to Table 6-5).

- The capsule formulation of NIR178 used in CNIR178X2103J study to establish the maximum tolerated dose (MTD) of NIR178 + PDR001 combination in advanced NSCLC patients differs from that used in CNIR178X2201 study with regards to excipients and their quantitative composition as well as manufacturing. The relative bioavailability between Novartis' capsule formulation (used in the present clinical study) and the one used in the first-in-human study CNIR178X2103J has not been determined. Preliminary analysis based on cross-study comparison of patient-level pharmacokinetic data did not show apparent differences in drug exposure following repeated dosing of NIR178 160 mg BID using these two formulations, therefore it is considered that the pharmacokinetic and safety profile of NIR178 240 mg BID + PDR001 in the current study will be consistent to that observed earlier in CNIR178X2103J study with the 240 mg BID dose.

PDR001 is being tested in an ongoing, multicenter, open-label study CPDR001X2101 with a phase I dose escalation part followed by a phase II part. The recommended phase II dose was declared as 400 mg every 4 weeks.

For further information, please refer to Section 1.2.2.2.

[redacted]

2.4 Rationale for choice of combination drugs

In preclinical studies, NIR178 combination with either an anti PD-L1 or an anti-PD-1 antibody increases interferon gamma secretion of selected tumors synergistically. The synergism of anti-PD1 antibody and NIR178 has been assessed in MC38 syngeneic tumor models. Furthermore, NIR178 as a single agent and in combination with PDR001 appears to have a manageable safety profile and preliminary signs of clinical activity, based on data from an ongoing phase Ib study in patients with advanced NSCLC, supporting further evaluation of this combination clinically in other tumor types.

2.4.1 Potential for drug interactions

Drug-drug interaction (DDI) between NIR178 and PDR001 are not expected although specific studies have not been conducted.

As an antibody, PDR001 is eliminated through protein catabolism and target-mediated disposition. Therefore, PDR001 is not anticipated to be directly eliminated through hepatic/renal metabolism and excretion or to compete with the elimination of NIR178, which is likely eliminated through metabolism. However, immunomodulatory drugs may induce systemic cytokines that alter CYP-mediated metabolism and affect the clearance of small molecules (Harvey et al 2014, Girish et al 2011). Therefore, the risk of DDI between PDR001 and the NIR178 cannot be totally excluded. For nivolumab, the Clinical Pharmacology and Biopharmaceutics Review (Nivolumab FDA application (2014)) states that nivolumab did not affect CYP enzyme-related cytokine modulation at doses as high as 10 mg/kg in patients. Nevertheless, concentration measurements of NIR178 in the presence of PDR001 are evaluated in CNIR178X2103J study and will be evaluated in this study to explore a possible pharmacokinetic drug interaction between PDR001 and combined drugs.

2.5 Rationale for choice of comparators drugs

Not applicable.

[redacted]

2.6 Risks and benefits

Appropriate eligibility criteria, as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.2 and Section 6.3. The risk to patients in this study may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, and stopping rules.

While the incidence of immune related adverse events with single agent PD-1 inhibitors has been well characterized, there may be a higher incidence of immune related adverse events with combination immune therapies, including the combination of NIR178 + PDR001. These immune-mediated adverse events may be serious and may include, but are not limited to, pneumonitis, hepatitis, severe cutaneous adverse reactions, endocrine disorders and other autoimmune disorders. Given that responses to single agent PD-1/PDL-1 inhibitors can be improved upon with combinations of IO therapies, the combination of NIR178 and PDR001 is hypothesized to improve the response to existing standard of care therapies in the tumors being evaluated in this study. The encouraging tolerability and response rates observed in the ongoing phase Ib study of NIR178+PDR001 in advanced NSCLC in both immunotherapy exposed and naive patients lends support to this hypothesis. Therefore, the benefit of the combination of NIR178 + PDR001 is thought to outweigh the risk in patients with advanced malignancies being evaluated in this study.

No substantial additional risk for patients' safety due to the SARS-CoV-2 virus and the COVID-19 pandemic has been identified at this time and therefore the benefit risk remains unchanged. In case of active COVID-19 infection, a careful benefit risk evaluation will be performed to determine whether patients can remain on study treatment or not.

For additional information on risk-benefit assessment, please refer to [NIR178 (PBF-509) Investigator’s Brochure] and [PDR001 Investigator’s Brochure].

[redacted]

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
Part 1:To evaluate the efficacy of NIR178 and PDR001 combination in patients with selected advanced solid tumors and diffuse large B cell lymphoma (DLBCL)	Overall Response Rate (ORR) by RECIST v1.1 (for solid tumors) or Cheson (for DLBCL) or PCWG3 criteria for mCRPC (Appendix 5)	Refer to Section 10.4.
Part 2: To assess the efficacy of continuous and several intermittent dosing schedules of NIR178 in combination with PDR001 in NSCLC	Overall Response Rate (ORR) by RECIST v1.1 (for solid tumors)	
Part 3: To evaluate efficacy of intermittent or continuous dosing schedule of NIR178 in one or two selected tumor types	Overall Response Rate (ORR) by RECIST v1.1 (for solid tumors) or Cheson (for DLBCL) or PCWG3 criteria for mCRPC (Appendix 5)	
Secondary		Refer to Section 10.5 and Appendix 3.
To assess efficacy of NIR178+PDR001 in select advanced solid tumors and lymphoma	Overall Response rate (ORR) by iRECIST and in addition, for mCRPC, best PSA change from baseline.	
To assess efficacy of NIR178+PDR001 in select advanced solid tumors and lymphoma	Disease Control Rate (DCR), duration of response (DoR), Progression Free Survival (PFS), 2 year Overall Survival (OS) rate by RECIST v1.1 and iRECIST (for solid tumors), Cheson (for DLBCL), and PCWG3 criteria for mCRPC (Appendix 5)	
To assess the safety and tolerability of the NIR178 and PDR001 combination using NIR178 hard gelatin capsule and FCT formulation	Frequency, severity and seriousness of AEs, laboratory abnormalities and other safety parameters. Dose interruptions, reductions and dose intensity.	
To characterize changes in the immune infiltrate in tumors	Change from baseline in TILs by immunohistochemistry (IHC) (such as CD8)	

[redacted]

Objective	Endpoint	Analysis
To characterize the pharmacokinetics (PK) of NIR178, its metabolite NJI765 and PDR001 in combination using hard gelatin capsule and FCT formulation	Plasma concentration time profiles of NIR178, NJI765 and PK parameters. Serum concentration time profiles of PDR001 and PK parameters	
To assess immunogenicity of PDR001	Presence and/or concentration of anti-PDR001 antibodies	
Japanese Safety Run-in:To assess the preliminary safety, and PK of single agent NIR178 and in combination with PDR001 in Japanese patients	Frequency, severity and seriousness of DLTs, AEs, laboratory abnormalities and other safety parameters (ECG, physical exams etc). Plasma concentration time profiles of NIR178/PDR001 and PK parameters.	
[redacted]		

[redacted]

4 Study design

4.1 Description of study design

This is an open-label multi-part, phase II study evaluating the combination of NIR178 and PDR001 in patients with advanced solid tumors and diffuse large B cell lymphoma (DLBCL). Patients will receive treatment with the combination until disease progression (assessed by investigator per iRECIST (Appendix 3) or Cheson et al (2014) for DLBCL), unacceptable toxicity, start of a new anti-neoplastic therapy, or discontinuation at the discretion of the investigator or patient, lost to follow-up, death or study is terminated by the sponsor. All patients who discontinue from study treatment due to disease progression must have their progression clearly documented. All disease assessments will be performed locally by the investigator.

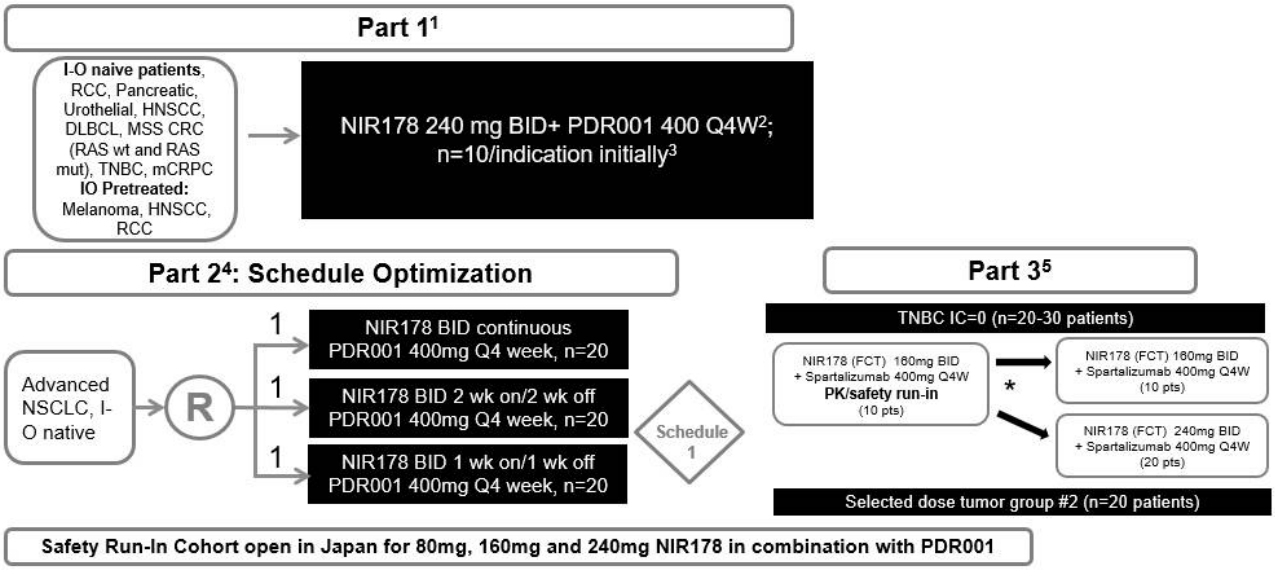
Submission of a pre-treatment and on-study tumor sample is mandated for all patients enrolled. The timing of the sample collection will be: 1) A pre-treatment biopsy (defined as obtained after most recent therapy and within 6 months preceding first dose of study treatment 2) on-treatment tumor biopsy taken on C2D15 (+15 days). Exceptions may be made on a case by case basis after discussion between Novartis and the Investigator. An optional biopsy may be collected at end of treatment and at disease progression when patients continue on study treatment due to overall clinical benefit.

This phase II study has 3 parts (Figure 4-1). Parts 1 and 2 will enroll in parallel, and Part 3 will open once results from Parts 1 and 2 are available. As of protocol amendment 6, Part 3 will be opened in parallel with Part 1, using the NIR178 continuous dosing schedule, which was identified as the preferred dosing schedule in Part 2 of the study.

- Part 1: Multi-arm Bayesian adaptive signal finding design in 13 groups (some of which in subgroups based on mutation status or prior treatment), and diffuse large B cell lymphoma (DLBCL) with continuous dosing of NIR178 in combination with PDR001.
- Part 2: Exploration of continuous and intermittent NIR178 schedules in combination with PDR001 in patients with advanced non-small cell lung cancer (NSCLC).
- Part 3: Further evaluation of optimal intermittent or continuous schedule of NIR178 in combination with PDR001 (if selected based on results of Part 2). As of protocol amendment 6, Part 3 will explore the safety and pharmacokinetics of the FCT formulation of NIR178 continuous dosing in combination with PDR001 in TNBC patients. A second tumor group may be considered for Part 3 following analysis of data from Part 1.
- In addition, a safety run-in part will be conducted in Japanese patients with tumor types specified in parts 1,2 and 3, in order to evaluate the safety and pharmacokinetic profiles of NIR178 as a single-agent or in combination with PDR001(Section 4.1.4 and Figure 4-2).

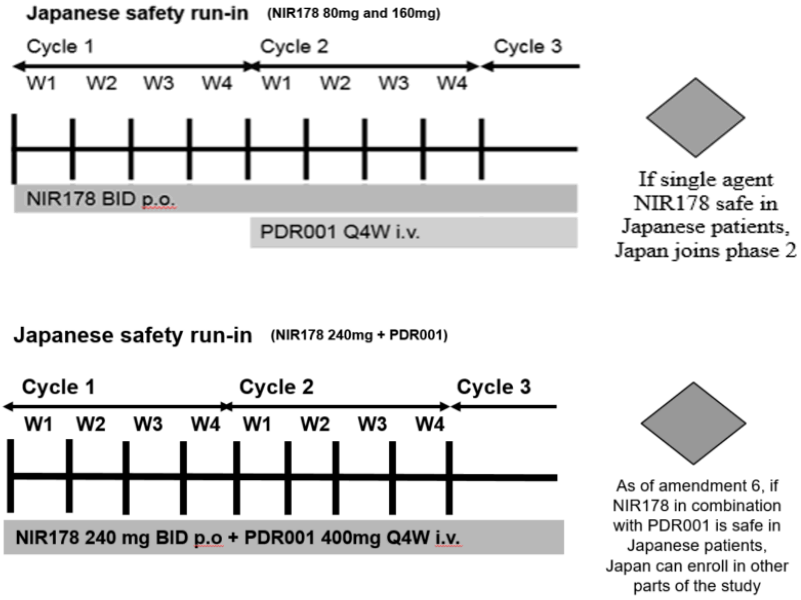
[redacted]

Figure 4-1 Study design



- [1]Part 1: Bayesian adaptive signal finding in patients
- [2]Prior to Amendment 5, all patients were treated with NIR178 160mg BID + PDR001 400mg Q4W
- [3]Interim analysis of ORR using Bayesian adaptive model, Tumors in which treatment is not declared futile continue enrolling up to 30 patients (except for MSS CRC, 20 additional patients will be enrolled in each tumor group (RAS wildtype and RAS mutant))
- [4]Part 2: NIR+PDR Schedule optimization
- [5]Part 3: The selected groups will be based on emerging data from part 1, part 2 and latest scientific literature
- * Dose increment criteria to complete part 3 at 160mg BID or increase to 240mg BID

Figure 4-2 Study design- Japanese run-in part (NIR178 Single Agent and NIR178 +PDR001)



4.1.1 Part 1: Bayesian adaptive signal finding in solid tumors and DLBCL

Part 1 of the study will enroll patients in the following tumor groups: renal cell carcinoma (RCC) (IO naive and IO pretreated), pancreatic cancer, urothelial cancer, squamous cell carcinoma of head and neck cancer (HNSCC) (IO naive and IO pretreated),, diffuse large B-cell lymphoma (DLBCL), microsatellite stable colorectal cancer (MSS CRC) (RAS wildtype and RAS mutant), triple negative breast cancer (TNBC), cutaneous melanoma (BRAF V600E) and metastatic castration resistant prostate cancer (mCRPC). Each tumor type will initially enroll at least 10 patients (with minimum requirements described in Section 4.2). Depending on whether or not pre-specified criteria for futility are met, each tumor group may enroll up to a maximum of 30 patients with the exception of the MSS CRC RAS mutant and RAS wildtype groups, in which 20 additional patients will be enrolled per group. Therefore, this part will enroll a minimum of 130 patients and may enroll a maximum possible total of 310 patients.

Accrual to each tumor type in Part 1 will based on futility analyses of observed ORR rates via interim analyses (for details of timing on interim analysis, see Section 4.2). These analyses will allow borrowing of information across tumor types with a hierarchical model (see Section 10). The hierarchical model allows dynamic borrowing of information between groups such that more borrowing occurs across the groups that have similar ORR and less borrowing between groups which differ. In this way, the model is a compromise between the two alternate extremes of either a completely pooled analysis or a separate analysis in each group.

4.1.2 Part 2: NIR178+PDR001 schedule optimization

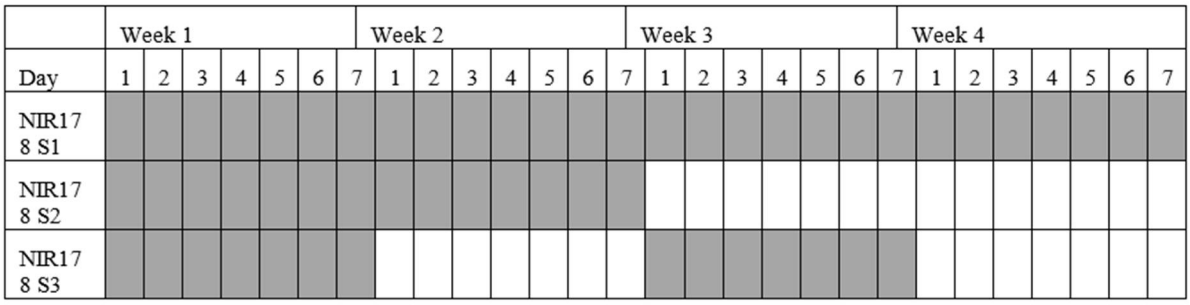
Part 2 of the study will enroll only patients with advanced/metastatic NSCLC who are naïve to prior immunotherapy. Eligible patients will be randomized in a 1:1:1 fashion to one of 3 groups, each evaluating a different dosing schedule of NIR178 within a 28 day cycle (Figure 4-3). The dosing schedule of PDR001 will be the same in each group (400mg IV every 28 days). Randomization will be done in order to balance covariates across the three different groups. Given the known correlation between PD-L1 expression and response to PD-1 inhibitors in NSCLC, the treatment groups will be analyzed retrospectively according to baseline PD-L1 expression (present/absent) defined by expression levels <1% or > 1% by immunohistochemistry (IHC).

[redacted]

Three schedules of NIR178 will be evaluated in parallel in combination with PDR001 (Figure 4-3):

- NIR178 S1: BID continuous
- NIR178 S2: BID 14 days on/14 days off
- NIR178 S3: BID 7 days on/7 days off

Figure 4-3 Alternate NIR178 dosing schedules within one cycle



Each NIR178 dosing group will enroll 20 patients (total 60 patients). The safety, tumor response rates, and tumor immune modulation of the intermittent NIR178 schedules (NIR178 S2 and S3) will be compared to that in the continuous schedule (NIR178 S1). Based on cumulative data (including safety, tolerability, preliminary anti-tumor activity, PK, and PD) across the three schedules, an intermittent dosing schedule may be selected by Novartis for further evaluation in Part 3 of the study after documented discussion with study investigators.

4.1.3 Part 3: NIR178+PDR001 additional exploration in selected tumor types

Part 3 of the study will be an expansion of an intermittent or continuous NIR178 dosing schedule (if selected) and further evaluation of safety, efficacy, and immune modulation of the alternate NIR178 schedule in combination with PDR001 in one or two tumor groups of 20 patients each. If Part 3 is initiated, a total of 50 patients would be enrolled to this part. The one or two tumor groups in Part 3 will be selected based on the emerging data from Part 1 and Part 2. If one of the tumor groups selected for Part 3 is NSCLC, this group will enroll patients previously exposed to immunotherapy.

Novartis may decide to not open Part 3 for enrollment based on emerging data from Part 1 and Part 2.

As of Protocol Amendment 6, TNBC is one of the selected tumor groups and will enroll patients with a known PD-L1 SP142 status of IC=0 (<1%). Part 3 of the study will evaluate continuous BID NIR178 dosing schedule using the FCT NIR178 formulation. In specific, evaluation of safety, efficacy, and immune modulation of the continuous NIR178 schedule in combination with PDR001 will be performed in the TNBC tumor group which will consist of 20-30 patients. An additional tumor group may be considered for Part 3 which may enroll 20 patients.

Part 3 of the study will start with the FCT formulation of NIR178 at 160mg BID in combination with PDR001 400mg Q4W as a PK/safety run-in part. After the first 10 patients complete at least 1 cycle, a safety analysis will be conducted to decide whether to increase the NIR178 dose

[redacted]

to 240mg BID or complete Part 3 with NIR178 160mg BID. The dose increment criteria is as follows:

- If < 2 patients of the 10 evaluable patients have Grade 3/4 AEs suspected to be related study drug with 1 cycle of study treatment, dose escalate to 240 mg BID and enroll 20 additional patients
- If 2 or 3 patients of the 10 evaluable patients have Grade 3/4 AEs suspected to be related study drug with 1 cycle of study treatment, 10 more patients will be enrolled at 160 mg BID
- If > 3 patients of the 10 evaluable patients have Grade 3/4 AEs suspected to be related study drug with 1 cycle of study treatment, no additional patients will be enrolled and development of the FCT formulation will be reassessed.

Cumulative data (including safety, tolerability, preliminary anti-tumor activity, PK, and PD) will be reviewed on an ongoing basis by Novartis and study investigators via teleconferences.

4.1.4 Japanese safety run-in part

A separate safety run-in part will be conducted in Japan in order to adequately characterize the safety and pharmacokinetic profiles of NIR178 as a single-agent (Figure 4-2). Patients enrolled in this part will be excluded from the primary analysis for efficacy and will also be exempt from the mandatory paired biopsy requirement.

Patients enrolled in the safety run-in part must be hospitalized for the first cycle of therapy for safety monitoring. Patients will receive NIR178 as single agent for the first cycle (28 days). If the patients complete cycle 1 without experiencing DLTs (see Table 6-3), they will initiate combination therapy with PDR001 400mg IV q4weeks starting cycle 2 onwards, and continue at the same dose of NIR178. Patients who experience a DLT in cycle 1 will be permanently discontinued from the study treatment and will not proceed to combination therapy. Patients will continue on combination therapy until they experience unacceptable toxicity, confirmed disease progression per iRECIST or Cheson et al (2014) for DLBCL and/or treatment is discontinued at the discretion of the investigator or the patient.

As of Amendment 6, newly enrolled patients in the Japanese safety run-in will receive NIR178 240mg BID in combination with PDR001 400mg IV Q4W starting Cycle 1 day 1. If the patients complete cycle 1 without experiencing DLTs, they will continue on the same combination therapy of NIR178 and PDR001.

In the CPDR001X1101 study of single agent PDR001 in Japanese patients, the safety and PK of PDR001 for Japanese patients were similar between Japanese and non-Japanese patients and the recommended dose determined for PDR001 in non-Japanese patients was found to be acceptable for Japanese patients. Therefore, the dose for PDR001 in the safety run-in part will be 400 mg IV Q4 weeks.

The period for evaluating DLTs will be cycle 1 (i.e. the first 28 days of treatment with single agent NIR178). **Patients must complete a minimum of** 80% of planned therapy during cycle 1 **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. Dose escalation decisions will occur when the cohort of patients has met these criteria**. Upon comprehensive review of all available safety, PK, and PD data (including that of the

[redacted]

combination therapy phase), Novartis in conjunction with the Japanese study investigators will determine if additional patients in Japan can join the phase II study. The safety run-in will evaluate two NIR178 dose levels sequentially. Each dose level may consist of 3 to 6 newly enrolled patients who have tumor histologies specified in Section 5, and meet all other inclusion/exclusion criteria.

1. NIR178 80mg BID continuously (-1 dose level)
2. NIR178 160mg BID continuously

The first three patients enrolled to the NIR178 80mg dose level will be observed for a full cycle of treatment with NIR178 before additional patients are enrolled. All patients will have enrollment staggered by at least 24 hours.

- If one patient experiences a DLT at the NIR178 80mg dose level, the safety run-in part will be terminated and Japanese patients will not join the phase II study.
- If 0/3 patients at 80mg experience a DLT in cycle 1, evaluation of the 80 mg dose level will be complete and the next dose level (160mg BID) with single agent NIR178 or (160 mg BID) or NIR178 240 mg in combination with PDR001will be initiated with 3 new patients.
- If 0/3 patients at 160mg NIR178 experience a DLT in cycle 1, NIR178 160mg dose in combination with PDR001 may be declared safe in Japanese patients upon review of all available safety, PK, and PD data, and Japanese patients may join the phase II part of the study.
- If 1 out of 3 patients experience a DLT at 160mg NIR178 during cycle 1, 3 additional patients will be enrolled to this dose level. If no more than 1 out of 6 patients experience DLT during cycle 1 at the 160mg dose, NIR178 in combination with PDR001 may be declared safe upon comprehensive review of the all available safety, PK, and PD data, and new Japanese patients may directly join the phase II part of the study.
- If more than 1 DLT occurs at the 160mg dose level of single agent NIR178 during cycle 1, the safety-run-in part will be terminated and Japanese patients will not join the phase II part of the study.

Patients who do not complete at least 80% of planned therapy during cycle 1 for reasons other than interruption/discontinuation due to AEs (e.g. Due to disease, progression or withdrawal of consent) will be replaced. If the 160mg dose of NIR178 in combination with PDR001 is declared well-tolerated (based on the observed DLTs and other available safety data), patients at the 80mg dose level who have completed at least 2 cycles of combination therapy with PDR001 without grade 2 or higher treatment related toxicity, may be allowed to escalate the NIR178 dose to 160mg after documented discussion with Novartis.

Based on the data from the Japanese safety run-in at the 80 mg and 160 mg NIR178 doses, no obvious ethnic differences on safety and pharmacokinetics were observed as compared with the data from non-Japanese patients who were enrolled in CNIR178X2103J and CNIR178X2201. Therefore, Japanese patients can join other parts of this study.

As of Amendment 6, Japanese patients in safety run-in will receive NIR178 240mg BID in combination with PDR001 starting cycle 1.

[redacted]

- If 0/3 patients at NIR178 240mg in combination with PDR001 experience a DLT in cycle 1, NIR178 240mg dose in combination with PDR001 may be declared safe in Japanese patients upon review of all available safety, PK, and PD data, and Japanese patients may join the other parts of the study.
- If 1 out of 3 patients experience a DLT at 240mg NIR178 in combination with PDR001 during cycle 1, 3 additional patients will be enrolled to this dose level. If no more than 1 out of 6 patients experience DLT during cycle 1 at this dose, NIR178 in combination with PDR001 may be declared safe upon comprehensive review of all the available safety, PK, and PD data, and new Japanese patients may directly join the other parts of the study.
- If more than 1 DLT occurs at the dose level of 240mg NIR178 in combination with PDR001 during cycle 1, the safety-run-in part will be terminated and Japanese patients will not join the rest of the study.

4.2 Timing of interim analyses and design adaptations

4.2.1 Part 1: Bayesian adaptive signal finding in solid tumors and DLBCL

Given the adaptive enrollment model and signal finding nature of this part, multiple interim analyses will be performed to either stop early for futility or enroll patients until the next Interim Analysis (IA) is performed or a maximum of 30 patients per group or 20 additional for each MSS CRC RAS wildtype and RAS mutant in that tumor type has been enrolled.

The first interim analysis (IA) will occur when at least one tumor type has accrued 10 patients who have at least one post-baseline disease assessment except for MSS-CRC RAS wildtype, MSS-CRC RAS mutant and RCC IO naive at 240 mg patients, in which no interim analysis will be done

Futility analyses at this and subsequent interim analyses will inform a “go/no-go" decision (to continue enrolling up to the maximum sample size allowed) for each tumor type based on dynamic borrowing of ORR data across tumor types (See Section 10).

For the purpose of the IA, if a patient is still on study and the last available efficacy assessment is a PR/CR which is yet to be confirmed by a subsequent scan, then this patient will be considered as a responder.

Subsequent IAs occur when one or more additional tumor types accrue 10 patients at the same dose level (with minimum requirements described before). While all available data will be used from all tumor types, the decision to stop early at the IA will be made only for tumor types with the minimum sample size requirement described above. Novartis will have the flexibility to choose IA time points if it appears that multiple tumor types may qualify for IA requirements within a reasonable time between them. The futility analysis will not be binding (even when the ORR-based early stopping criteria is met at an IA for a tumor type, Novartis along with investigators may decide to continue enrolling patients to that particular tumor type if comprehensive review of all available data suggests that the patients are receiving clinical benefit).

[redacted]

Japanese safety run-in:

No interim analysis is planned for this part. The decision for dose escalation and to allow participation in phase II part of the study will be based on all available safety data and the recommendation of participating investigators in Japan. Refer to Section 4.1.4.

4.3 Definition of end of study

The study will end when all patients have completed the treatment period and 150-day safety follow-up after the last dose of PDR001 or 30 days after the last dose of NIR178 whichever occurs later, and at least 80% of patients have completed at least 24 months of survival follow up from start of study therapy. Additionally, if another clinical study becomes available that can continue to provide study treatment in this patient population, all patients ongoing are transferred to that clinical study and all discontinued patients have completed the safety follow-up period. The follow-up for disease progression and survival will not be performed or pursued (see Section 7.1.5.1) At the end of the study, every effort will be made to continue provision of study treatment to patients who in the opinion of the investigator are still deriving clinical benefit through designated post-trial access programs or roll-over protocols, provided patient meets all eligibility criteria.

Refer to Section 10 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. Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, the patient should be seen as soon as possible for End of Treatment (EoT) visit and the same assessments should be performed as described in Section 7.1.3 for a discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Adult patients (≥ 18 years) with advanced or metastatic solid tumors or Diffuse Large B-cell lymphomas will be enrolled in the study.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. Patients who have completed the study may not be re-enrolled for a second course of treatment. Patients who do not initially meet all of the inclusion

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or exclusion criteria may be re-screened for consideration in the trial. If a patient is rescreened, the same patient ID number should be used.

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. Male or female patients ≥18 years of age.
   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.
2. Histologically documented advanced or metastatic solid tumors or lymphomas
   a. **Part 1**: histologically confirmed renal cell carcinoma (RCC), pancreatic cancer, urothelial cancer, head and neck squamous cell carcinoma (HNSCC), diffuse large B-cell lymphoma (DLBCL), microsatellite stable colorectal cancer (MSS CRC), triple negative breast cancer (TNBC), cutaneous melanoma or mCRPC
      - Patients with colorectal cancer must have microsatellite stable (MSS) disease as detected by PCR-based assay or loss of mismatch repair (MMR) protein expression by immunohistochemistry and confirmed RAS genotype by standard testing of tumor specimen based on local available laboratory data.
      - Patients with unresectable or metastatic cutaneous melanoma that have confirmed BRAF V600E status by standard testing of tumor specimen by local available laboratory data.
   b. **Part 2**: histologically confirmed diagnosis of advanced/metastatic NSCLC. For those with mixed histology, there must be a predominant histology
      - Patients should have confirmed EGFR and ALK genotype when clinically indicated and performed per standard testing of tumor specimen based on local laboratory data.
   c. **Part 3**: histologically confirmed diagnosis of selected advanced/metastatic malignancies should Part 3 be opened to enrollment. As of protocol amendment 6, Part 3 will open and enroll TNBC patients with PD-L1 SP-142 IC=0. A second tumor group may be considered for Part 3 following analysis of data from Part 1.
   d. **Safety run-in** part in Japanese patients can enroll any tumor type included in Parts 1, 2 and 3.
3. Patient (except for those participating in Japanese safety run-in) 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 screening, and again during therapy on this study. The use of a recent sample is permitted under the following conditions (both must be met):
   a. Biopsy was collected ≤ 6 months before 1st dose of study treatment
   b. No immunotherapy was given to the patient since collection of biopsy.
4. Part 1 – 3 only: Patients (other than those with DLBCL) must previously have received at least 1 and no more than 3 prior lines of therapy for their disease (with the exception of IO

[redacted]

pre-treated cutaneous melanoma, HNSCC and RCC), unless considered inappropriate for the patient (e.g. safety concerns, label contraindications):

- **MSS Colorectal Cancer (MSS CRC):**
  - Patients with MSS CRC must have received (or be intolerant to) prior therapy with fluoropyrimidine-oxaliplatin- and irinotecan- based regimens.
  - Patient with wild type RAS must have received prior treatment with an antibody targeting EGFR (e.g. cetuximab or panitumumab)
- **Triple Negative Breast Cancer (TNBC):**
  - Part 1: Patients with TNBC must have received a prior taxane- containing regimen.
  - Part 3:
    - Patients should have documented disease progression following, or intolerance to, no more than 2 prior lines of chemotherapy for advanced or metastatic disease. Neoadjuvant and/or adjuvant chemotherapy administered with curative intent will count as one prior line of therapy, if disease recurred within 12 months of the last treatment.
    - Patients must have received prior systemic treatment that included taxane-based chemotherapy for (neo) adjuvant or metastatic disease.
    - Patients should have a known PD-L1 status as per local available testing determined by VENTANA PD-L1 SP142 Assay with IC score of 0 (<1%).
- **Urothelial Cancer:**
  - Patients with urothelial cancer must have received a prior platinum-containing regimen or be ineligible for cisplatin.
- **Renal Cell Carcinoma (RCC):**
  - IO Naive RCC: Patients with RCC must have received a prior VEGF tyrosine kinase inhibitor (TKI).
  - IO pre-treated RCC: Patients with RCC with no more than 2 prior lines of therapy. Patient must have received a prior VEGF TKI and have been pretreated with an anti-PD-1/PD-L1 as a single agent or in combination
- **Head & Neck Squamous Cell Carcinoma (HNSCC):**
  - IO Naive HNSCC:
    - Patients with HNSCC with no more than 3 prior lines of therapy. Patient must have received a prior platinum-containing regimen and have not been previously treated with any anti-PD1/L1 agents in single agent/combinations.
  - IO pre-treated HNSCC:
    - Patients with HNSCC with no more than 2 prior lines of therapy. Patient must have received a prior platinum-containing regimen and have been pretreated with an anti-PD-1/PD-L1 as a single agent or in combinations
- **Cutaneous Melanoma**

[redacted]

- Patients must previously have received at least 1 and no more than 2 prior lines of therapy.
- BRAF V600E wild type patients: must have received anti-PD-1/PD-L1 single-agent, or in combination with anti-CTLA-4 therapy
- BRAF V600E mutant patients: must have received prior anti-PD-1/PD-L1 single-agent, or in combination with anti-CTLA-4 therapy. In addition, subjects must have received prior BRAF V600E inhibitor therapy, either single-agent or in combination with a MEK inhibitor

- **Metastatic Castration Resistant Prostate Cancer (mCRPC):**
  - Of the 1-3 prior lines of therapy, patients must have received and failed at least one line of treatment after emergence of castration resistant disease
- **Diffuse Large B-Cell Lymphoma (DLBCL):**
  - Patients with DLBCL should be limited to those with no available therapies of proven clinical benefit.
  - Patient should have had prior autologous hematopoietic stem cell transplantation (auto-HSCT) or determined to be ineligible for auto-HSCT.
- **Non-Small Cell Lung Cancer (NSCLC):**
  - Patients with NSCLC must have received a prior platinum-based combination.For patients with NSCLC, EGFR mutation with exon 19 deletion or L858R mutation (Exon 21) or anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangement positive must have failed prior Tyrosine-kinase inhibitor (TKI) therapy
  - Patients with EGFR positive NSCLC with a T790M mutation must have progressed on osimertinib or discontinued due to toxicity.

5. If one of the tumor groups selected for Part 3 is NSCLC, this group will enroll patients previously exposed to immunotherapy. *(In protocol amendment 4, this inclusion criteria has been incorporated as part of inclusion criteria #4.)* Patients with DLBCL should be limited to those with no available therapies of proven clinical benefit
   - Patients should have had prior autologous hematopoietic stem cell transplantation (auto-HSCT) or determined to be ineligible for auto-HSCT.
6. Patients must not have received prior immunotherapy (previous immune checkpoint inhibitors; single agent and/or combination therapy with anti-CTLA-4, anti-PD-1, anti-PD-L1), with the exception of cutaneous melanoma, IO pre-treated HNSCC and IO pre-treated RCC in part 1, NSCLC patients enrolled in Part 3 and Japanese safety run-in part.
7. *(In protocol amendment 4, this inclusion criteria has been incorporated as part of inclusion criteria #4.)* For patients with NSCLC, EGFR mutation with exon 19 deletion or L858R mutation (Exon 21) or anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangement positive must have failed prior Tyrosine-kinase inhibitor (TKI) therapy.

[redacted]

8. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as >20 mm with conventional techniques or as >10 mm with spiral computer tomography (CT) scan, Magnetic Resonance Imaging (MRI), or calipers by clinical exam.
   Note: If prior treatment was discontinued due to toxicity, patient must have continued evidence of measurable or evaluable disease.
9. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
10. Written informed consent must be obtained prior to any screening procedures. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.

5.3 Exclusion criteria

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

1. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
2. History of another primary malignancy except for:
   - Malignancy treated with curative intent and with no known active disease ≥2 years before the first dose of study drug and of low potential risk for recurrence
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without evidence of disease
3. Active or prior documented autoimmune disease within the past 2 years
   NOTE: Patients with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
4. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
5. History of interstitial lung disease or non-infectious pneumonitis
6. History of primary immunodeficiency
7. History of allogeneic organ or stem cell transplant
8. Ongoing or prior treatment with A2aR inhibitors. Patients previously treated with A2aR inhibitors for non-oncologic indications (e.g. Parkinson's disease) may be considered for enrollment on a case by case basis.
9. More than 2 or 3 prior lines of therapy (as indicated for each tumor type in the inclusion criteria 4), except for Japanese safety run-in part and DLBCL patients.
10. 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, 6 weeks is indicated as washout period. For patients receiving anticancer immunotherapies, 4 weeks is indicated as the washout period. GnRH therapy to maintain effective testosterone suppression levels is allowed for mCRPC patients.

[redacted]

11. Non-palliative radiotherapy within 2 weeks prior to the first dose of study drug. Palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass is allowed. To allow for assessment of response to treatment, patients must have remaining measurable disease that has not been irradiated.
12. 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).
13. Current or prior use of immunosuppressive medication within 28 days before the first dose of PDR001, with the exception of intranasal/inhaled corticosteroids or systemic corticosteroids at physiological doses (not exceeding equivalent of 10 mg/day of prednisone)
14. Any of the following clinical laboratory results during screening (i.e., within 21 days before the first dose of study treatment):
    - Absolute Neutrophil Count <1.0 x 10^9/L
    - Platelets <100 x 10^9/L (for DLBCL patients platelets < 75 x 10^9/L)
    - Hemoglobin (Hgb) <9 g/dL (for DLBCL patients Hgb < 8g/dL)
    - Serum creatinine >1.5 mg/dL OR Creatinine Clearance < 45 mL/min using Cockcroft-Gault formula (Appendix 6)
    - Total bilirubin >1.5 x Upper limit of normal (ULN)
    - Aspartate transaminase (AST) > 3 x ULN
    - Alanine transaminase (ALT) > 3 x ULN
15. Mean QT interval corrected for heart rate (QTcF) ≥470 ms calculated from 3 electrocardiograms (ECGs – in triplicate ≥1 minute apart)
16. Any unresolved toxicity (>Common Terminology Criteria for Adverse Events (CTCAE) grade 2) from previous anti-cancer therapy. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy)
17. History of severe hypersensitivity to any ingredients of study drug(s) and other monoclonal antibodies and/or their excipients. Patients previously exposed to anti-PD-1/PD-L1 treatment who are adequately treated for skin rash or with replacement therapy. Changes to the protocol for endocrinopathies should not be excluded
18. Uncontrolled concurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that in the investigator's opinion would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
19. Known history of previous clinical diagnosis of tuberculosis
20. History of leptomeningeal carcinomatosis
21. Receipt of any live vaccine within 4 weeks prior to study entry or within 4 weeks of receiving PDR001 or NIR178

[redacted]

22. Pregnant or nursing (lactating) women
23. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
24. Smoking (e.g. cigarettes, cigars and pipe) must be discontinued at least 7 days prior to initiating study drug administration; smoking cessation products (e.g transdermal nicotine patches or chewing gum) may be used.
25. Concurrent administration of strong inhibitors or moderate inducers of CYP1A2 is not permitted; administration must be discontinued at least 7 days prior to initiating study drug administration
26. Concurrent administration of sensitive and narrow therapeutic index substrates of CYP1A2 is not permitted; administration must be discontinued at least 7 days prior to initiating study drug administration
27. History of severe hypersensitivity reactions, which in the opinion of the investigator may pose an increased risk of serious infusion reaction.
28. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents ≤ 2 weeks prior to start of study treatment. If erythroid stimulating agents were initiated more than 2 weeks prior to the first dose of study treatment and the patient is on a stable dose, they can be maintained.
29. History or current diagnosis of cardiac disease indicating significant risk of safety for patients participating in the study such as uncontrolled or significant cardiac disease, including any of the following:
    - recent myocardial infarction (within last 6 months),
    - uncontrolled congestive heart failure,
    - unstable angina (within last 6 months),
    - clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker).
30. Specific underlying conditions for oral agents. For example: impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral NIR178 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection or presence of more than or equal to Grade 2 toxicity (except alopecia) due to prior therapy)
31. 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 or 30 days after the last dose of NIR178, whichever occurs later. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. 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

[redacted]

- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

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

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate [generally age from 40 to 59 years], history of vasomotor symptoms [e.g. hot flush]) 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.

32. Sexually active males unless they use a condom during intercourse while taking drug and 30 days after stopping NIR178. Sexually active males should not father a child in this period.

6 Treatment

6.1 Study treatment

For this study, the investigational drugs are NIR178 and PDR001. The study treatment is defined as NIR178 in combination with PDR001. Please note that additional dosage strengths for any of the study drugs may become available. They will be given as the following dose strength and forms:

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen		
NIR178	40mg, 80mg and/or 160mg capsules for oral use	160mg, 240mg*	Part 1	Part 2	Part 3
			Continuous BID	Continuous and intermittent BID per randomization	Continuous or intermittent BID based on Part 1 and Part 2 results
NIR178**	80mg, 240mg Film-coated tablet for oral use	160mg 240mg	Not applicable	Not applicable	Continuous BID
PDR001	100mg powder for solution for infusion	400mg	Every 4 weeks		

*All newly enrolled patients under Amendment 5 will receive NIR178 240mg BID

**As of Protocol Amendment 6, patients enrolled in Part 3 will receive continuous dosing of NIR178 FCT in combination with PDR001

[redacted]

NIR178

NIR178 will be administered at 160 mg orally twice daily (BID) either continuously or based on the assigned intermittent dosing schedule. As of Amendment 5, all newly enrolled patients will be treated with NIR178 240mg BID. As of amendment 6, in Part 3 of the study, NIR178 FCT will be administered orally twice daily (BID) on a continuous dosing schedule starting with a dose of 160 mg BID, that may be increased to 240 mg BID based on safety and pharmacokinetic data available after the initial 10 patients are treated.

Patients should take NIR178 twice daily at approximately the same time each day in the morning and evening and should ensure there is an approximate 12-hour interval between each daily dose. On days that PK samples are obtained, the patient should take NIR178 during the clinic visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff. The patient should not take the morning dose of NIR178 at home during inpatient visits, particularly in those with PK assessments.

Patients should take NIR178 on an empty stomach (i.e. fast from food and drink, except water) at least 1 hour before or 2 hours after a meal. Each dose may be taken with a glass of water (approximately 8 ounces or approx. 235 mL). An ongoing clinical study (CNIR178X2103J) in NSCLC patients includes an investigation of the impact of food on NIR178 PK. If the results of this study indicate that NIR178 may be taken with or without regard to food, the fasting requirement may be removed and administration instructions will communicated in writing by Novartis.

Patients should be instructed to swallow whole capsules or tablets and not to chew or open them.

If vomiting occurs during the course of treatment, patients should not take the study drug (NIR178) again before the next scheduled dose.

Patients should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 4 hours after the approximate time of the usual daily dosing. That day's dose should be omitted and the patient should continue treatment with the next scheduled dose.

PDR001

PDR001 will be administered via IV infusion over 30 minutes once every 4 weeks. Infusions of PDR001 can be extended to up to 2 hours if clinically indicated.

Further instructions for the preparation and dispensation of NIR178 and PDR001 are described in the CNIR178X2201 Pharmacy Manual.

Both study drugs will be administered on the same day. The first doses of the combination of NIR178 and PDR001 are administered at Cycle 1 Day 1, which defines the patient’s treatment cycles for the study. The start time of PDR001 infusion on dosing days can occur at any given time regardless of the dose administration schedule of NIR178.

All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Dose modifications and reductions should be followed described in Section 6.2.1 and Section 6.2.2.

[redacted]

6.1.1 Dosing regimen

Treatment cycle is defined as 28 days.

In Part 1 of the study, all patients will receive NIR178 240 mg twice daily continuously and 400 mg of PDR001 administered every 28 days (prior to Amendment 5, all patients were treated with NIR178 160 mg BID).

In Part 2 of the study, all patients will be randomly assigned to one of the three NIR178 dosing schedules in combination with PDR001:

1. NIR178 S1: Patients will take NIR178 160mg twice daily continuously with PDR001 400mg administered once on day 1, every 28 days.
2. NIR178 S2: Patients will take NIR178 160mg twice daily on days 1-14 of a 28 day cycle together with PDR001 400mg administered once on day 1 every 28 days.
3. NIR178 S3: Patients will take NIR178 160mg twice daily on days 1-7 and days 15-21 of a 28 day cycle together with PDR001 400mg administered once on day 1 every 28 days.

In Part 3 of the study, one or two tumor groups may be selected based on emerging data from Part 1 and Part 2.

As of protocol amendment 6, Part 3 will be opened in parallel with Part 1 to further assess TNBC patients with a PD-L1 SP-142 status of IC=0 (<1%) using NIR178 FCT formulation continuous dosing schedule in combination with PDR001. A second tumor group may be considered for Part 3 after completion of Part 1. The first 10 patients enrolled in Part 3 will receive a NIR178 dose of 160 mg BID FCT, and after all patients complete at least 1 cycle of treatment, safety and PK analysis will be performed to decide whether the dose should be increased to NIR178 240 mg BID FCT. If there is unexpected toxicity due to formulation change the dose will not be escalated to NIR178 240mg BID FCT and an additional 10 patients will be enrolled at NIR178 160mg BID FCT. If the NIR178 160mg BID FCT formulation is considered safe, dose escalation to NIR178 240 mg BID FCT will occur and an additional 20 patients will be enrolled.

In the Japanese safety run-in part, patients will take NIR178 at 80 or 160mg twice daily continuously during the Cycle 1, and then starting from Cycle 2D1, will receive NIR178 twice daily continuously in combination with PDR001 400mg administered once on day 1 every 28 days. The starting dose of NIR178 80mg is 50% of the RoW starting dose at which no DLT was observed in the CNIR178X2103J phase I/Ib study in combination with PDR001. As of protocol amendment 6, patients enrolled in the Japanese safety run-in part will receive NIR178 240mg twice daily in combination with PDR001 400 mg administered on day 1 of every 28 day cycles.

[redacted]

6.1.2 Ancillary treatments

Patients should not receive pre-medication to prevent an infusion reaction before the first infusion of study treatment, in order to determine if pre-medication is necessary. If a patient experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a patient experiences a Grade 3 anaphylactic/anaphylactoid reaction, the patient will be discontinued from the study. The patient may resume study treatment following documented discussion with the Novartis medical monitor. Guidelines on management of infusion reactions are provided in Table 6-2 (Recommended Dose Modifications).

The CTCAE category of "Infusion related reaction" should be used to describe study treatment related 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 study treatment until the patient experiences unacceptable toxicity, confirmed disease progression per iRECIST or Cheson et al (2014) for DLBCL patients or as per PCWG3 guidance (Appendix 5) for mCRPC and/or treatment is discontinued at the discretion of the investigator or the patient. The patients should not be withdrawn from the study due to progressive disease per RECIST v1.1 or Cheson et al (2014) only unless there is evidence suggesting lack of clinical benefit or clinical deterioration. If a patient has clinical or radiological evidence of disease progression but has evidence of 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 documented discussion with the Novartis medical monitor. In addition, treatment beyond disease progression should not jeopardize critical interventions to treat/prevent severe complications, or prevent patients from receiving adequate care (Section 7.1.2).

To account for possible late responses or responses with a prolonged immune-related tumor flare, patients with iRECIST or Cheson et al (2014) progression, ongoing during or at the end of treatment, may restart treatment if they experience a radiographic response following treatment discontinuation in the absence of interval treatment. Retreatment must begin within 4 weeks of the documented response. The schedule will be the same as the schedule being used prior to treatment discontinuation.

Patients who continue treatment beyond initial disease progression will continue all study procedures as outlined in Section 7. In case of clinical deterioration or suspicion of disease progression, a follow-up imaging assessment should be performed promptly rather than waiting for the next scheduled assessment. Patients with evidence of further disease progression on an imaging assessment or who are no longer deriving clinical benefit will be discontinued.

[redacted]

6.2 Dose modifications

6.2.1 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 for Clinical Oncology clinical practice guideline for Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy (Brahmer et al 2018) or the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Management of Toxicities from Immunotherapy (Haanen et al 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

NIR178 dose may be interrupted and/or reduced for treatment related adverse events during the course of treatment. For NIR178, dose reduction steps should follow guidelines outlined in Table 6-5. Dose reductions are not permitted for PDR001. PDR001 may be delayed due to toxicities. A patient must discontinue treatment with NIR178 and PDR001 if the toxicity recurs with the same or worse severity after treatment is resumed at a lower dose. **For Japanese safety run-in, dose reductions for NIR178 will not be allowed in the DLT observation period**.

Dose modifications/delays of NIR178 and PDR001 for specific adverse events are summarized in Table 6-2. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events and/or dose interruption periods as indicated in Table 6-2. However, in cases where a patient meeting criteria for permanent discontinuation due to a study treatment-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, the patient may continue treatment after documented discussion with Novartis. All dose interruptions/reductions of NIR78 and dose delays of PDR001 must be recorded on the Dosage Administration Record CRF.

PDR001 and NIR178 dosing may resume once the adverse event has resolved to the specified grade or better (as outlined in Table 6-2) or baseline. Patients unable to resume combination therapy after resolution of an adverse event may continue with either NIR178 or PDR001 as single agent, if the Investigator considers it to be in the patient's best interest to do so, following documented discussion with Novartis.

[redacted]

After a dose interruption, patients who are able to resume study treatment within the same treatment cycle (i.e. within 28 days of the last PDR001 dose) should resume dosing with NIR178 at the next scheduled dose within the same cycle. For AEs that resolve more than 28 days from the last dose of PDR001, both PDR001 and NIR178 must be restarted together with appropriate dose as soon as patient is able, and re-initiation of therapy must constitute the beginning of the next treatment cycle. Disease assessments will continue to occur at the frequency specified within the protocol (See Section 7.2.1), even if no longer in sync with cycle clock.

Non-immune related AEs (non-irAEs), resulting in dose delay of PDR001 or NIR178 lasting longer than 14 days will necessitate discontinuation of study drug. Exceptions may be made if the Investigator considers it to be in the patient's best interest to resume therapy, following documented discussion with Novartis. In the event of immune related AEs (irAEs) requiring treatment interruption, combination therapy with NIR178 and PDR001 can resume only when the specific irAE has resolved as outlined in Table 6-2, patient requires no more than physiologic dose of steroids (steroid equivalent of ≤ 10mg/day of prednisone), and patient has discontinued any other immunosuppressive drugs that were initiated for the irAE. Overall, for irAEs that do not recover to ≤ Grade 1 or baseline at a dose of immunosuppression of ≤ 10 mg/day prednisone or equivalent within 12 weeks after initiation of immunosuppressive therapy, and/or requiring continuation of other immunosuppressive drugs, PDR001 and NIR178 must be permanently discontinued (Figure 6-1).

Figure 6-1 Management of toxicity requiring dose interruptions

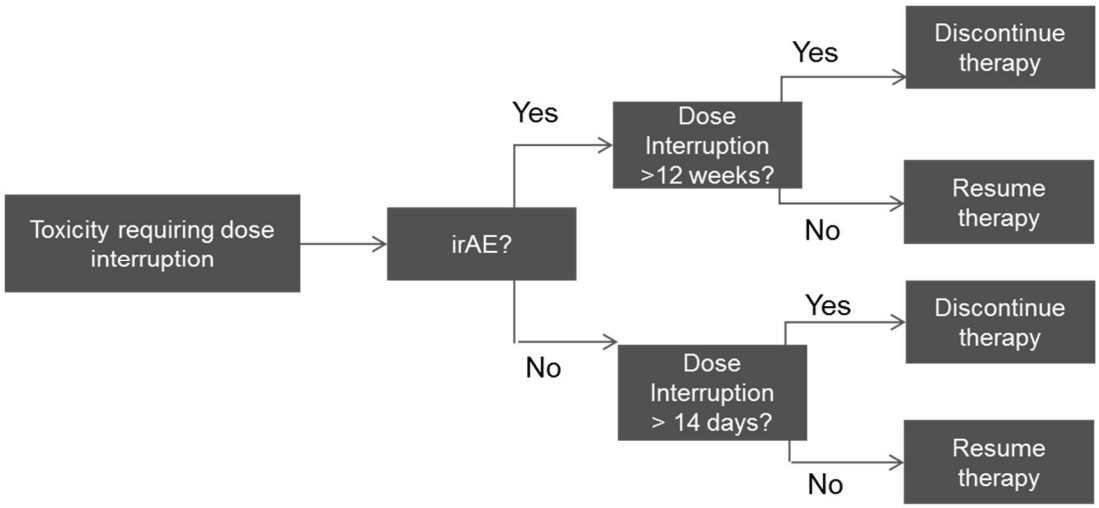

Table 6-2 Criteria for dose reduction / interruption and re-initiation of NIR178 and PDR001 treatment for adverse drug reactions

The instructions provided in this table and the criteria for dose reduction / interruption are used to determine a protocol deviation.

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
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.
Grade 3 and Grade 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.
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.

[redacted]

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Pulmonary (pneumonitis)	
Grade 1	Consider study treatment hold. Manage per institutional practice, consultation with pulmonologist is recommended. Consider resuming study treatment upon radiographic evidence of improvement.
Grade 2	Hold study treatment. Pulmonary and infection workup, consultation with pulmonologist is recommended. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification.
Grade 3 or Grade 4	Discontinue study treatment. Manage per institutional practice, consultation with pulmonologist is recommended.
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 the ECG(s) collected at screening.
Grade 4	Discontinue study treatment.
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.

[redacted]

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Gastrointestinal	
Diarrhea/colitis*	
Grade 1	May continue study treatment without dose modification. Manage per institutional standard guidelines which should 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.
Grade 3	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. After resuming treatment with NIR178, close monitoring with at least weekly LFTs is recommended for 1 cycle of treatment. If suspicion of autoimmune hepatitis, the following confirmatory diagnostic serological markers are recommended: Serum autoantibodies including antinuclear (ANA), smooth muscle antibody (SMA) or antibody to liver-kidney microsomes (anti-LKM), Immunoglobulin levels, total globulins, and when possible liver biopsy.
Grade 3 AST and/or ALT ALT or AST >3 x ULN and TBL >2 x ULN (or international normalized ratio [INR] >1.5) ALT or AST >3 x ULN and symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%])	Hold study treatment. Manage per institutional practices. Upon resolution to ≤ Grade 1 or baseline within 7 days, consider resuming PDR001 at the same dose and NIR178 at a lower dose after discussion with the Novartis Medical Monitor. After resuming treatment with NIR178, close monitoring with at least weekly LFTs is recommended for 1 cycle of treatment. Otherwise, discontinue study treatment. If suspicion of autoimmune hepatitis, the following confirmatory diagnostic serological markers are recommended: Serum autoantibodies including antinuclear (ANA), smooth muscle antibody (SMA) or antibody to liver-kidney microsomes (anti-LKM), Immunoglobulin levels, total globulins, and when possible liver biopsy.
Grade 4 AST and/or ALT	Discontinue study treatment.
Isolated total bilirubin elevation[**]	

[redacted]

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
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.
Combined elevations of AST or ALT and total bilirubin	
For participants with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0 x ULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis OR [AST or ALT >3x baseline OR > 8.0 xULN], whichever is lower, combined with [total bilirubin >2x baseline AND >2.0 x ULN] **Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin.	Mandatory: Interrupt treatment and adjudicate for DILI: Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs, or as clinically indicated, until AST, ALT, or total bilirubin have resolved ≤ ULN or to baseline. (Refer to the Section 6.2.2.1 for additional follow-up evaluations as applicable.) If causality assessment indicates that DILI is probable: Permanently discontinue participant from treatment. If not DILI: Treat the identified cause according to institutional guidelines. Once resolved, reduce by one dose level.
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.

[redacted]

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
Grade 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. May resume therapy following resolution or control with physiologic hormone replacement.
Grade 4	
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	

[redacted]

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
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.
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	

[redacted]

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
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.
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.

[redacted]

Worst toxicity CTCAE[a] grade	Recommended Dose Modification
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.
[a] Common Toxicity Criteria for Adverse Events (CTCAE)
*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.

Table 6-3 Criteria for defining dose limiting toxicities for the Japanese safety run-in part

For the purpose of Japanese safety run-in part, DLT defined as follows: **Any Grade 4 AEs are DLTs with the exception of:**	
	Neutropenia lasting ≤ 5 days that is not associated with fever or other clinical symptoms.
	Lymphopenia or Leukopenia.
	Electrolyte abnormalities that are not associated with clinical sequelae or deemed to be not clinically significant and are corrected with appropriate management or supplementation within 72 hours of the onset.
Any Grade 3 AEs are DLTs with the exception of:	
	Infusion reaction that resolves to ≤ Grade 1 within 6 hours.
	Nausea and vomiting that resolves within 2 days after starting optimal anti-emetic therapy.
	Thrombocytopenia without significant bleeding.
	Anemia grade 3 that resolves within 7 days in the absence of transfusion
	Diarrhea that resolves within 2 days after starting optimal anti-diarrhea treatment.
	Hypertension that resolves within 7 days after starting treatment.
	Infection or fever in the absence of neutropenia that resolves within < 5 days.
	Rash or photosensitivity that resolves within 7 days after starting treatment.
	Fatigue that resolves within 7 days.
	Immune-related adverse events that resolve within 7 days after starting treatment with corticosteroids.
The following Grade 2 AEs are considered DLTs:	
	Newly emerging total bilirubin ≥ 2 x ULN with ≥ CTCAE Grade 3 AST/ALT.
	Pneumonitis that does not resolve within 7 days after starting treatment with corticosteroids.
	Eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy OR requires systemic treatment.
	Other clinically significant toxicities, including a single event or multiple occurrences of the same event may be considered as DLTs.

[redacted]

6.2.2 Follow-up for toxicities

The emergence of Immune-Related AE (irAE) may be anticipated based on the mechanism of action of immunomodulatory therapies.

An irAE is any clinically significant adverse event affecting any organ that is associated with study drug exposure, is consistent with an immune-mediated mechanism, and where alternative explanations have been investigated and ruled out or are considered to be unlikely. Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator to verify the immune-related nature of the AE. An empiric trial of corticosteroids may also contribute to understanding the etiology of a potential irAE.

Consensus management algorithms for irAEs have been developed and are available to assist investigators in assessing and managing irAEs (refer to Section 6.2.1 Dose modifications).

Patients whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

All patients must be followed up for irAEs, AEs and SAEs for up to 150 days following the last dose of PDR001 or up to 30 days following the last dose of NIR178.

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

Patients with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI, and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

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

- For patients with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For patients with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT >3.0 x baseline] OR [ALT or AST > 8.0 x ULN], whichever occurs first, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, GLDH, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase.

[redacted]

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – e.g. using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, ERCP) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of the liver-specific ALP isoenzyme in patients with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (https://livertox.nih.gov/rucam.html).

Table 6-4 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Table 6-4 Clinical and Diagnostic assessments to rule out possible causes of LFT abnormalities

Disease	Assesment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon patients' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; CVD / ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

Obtain PK sample to determine exposure to study treatment and metabolites.

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes

[redacted]

of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented

6.2.3 Dose reduction steps for NIR178

Dose reduction steps for NIR178 are detailed in Table 6-5 based on the starting dose of 240 mg. Of the first 10 patients enrolled at the NIR178 240mg dose across all tumor types, if more than 33% of the patients experience grade 3 or higher suspected to be related adverse events, subsequent patients will start treatment at NIR178 160mg twice daily. Patients enrolled at the NIR178 240mg dose will be monitored on an ongoing basis for emerging toxicities.

Table 6-5 Dose reduction steps for NIR178

The following table should be used as a dose reduction guide for patients receiving NIR178 capsule formulation (hard gelatin capsules):

Dose reduction*				
	Starting dose level	**Dose level – 1**	**Dose level -2**	**Dose level – 3**
NIR178	240 mg	160 mg	120 mg	80mg**
*Dose reduction should be based on the worst toxicity demonstrated at the last dose. **Dose reduction below 80 mg is not allowed. Altering from initial dosing schedule for NIR178 is not allowed.				

The following table should be used as a dose reduction guide for patients receiving NIR178 160 mg or 240 mg BID film coated tablet (FCT) formulation:

Dose reduction*			
	Starting dose level	**Dose level – 1**	**Dose level – 2**
NIR178	240 mg	160 mg***	80 mg**
*Dose reduction should be based on the worst toxicity demonstrated at the last dose. **Dose reduction below 80 mg is not allowed. Altering from initial dosing schedule for NIR178 is not allowed. ***The first 10 patients enrolled in Part 3 of the study will be treated with the NIR178 160mg dose of the FCT formulation. A safety and PK analysis will be conducted to decide whether to increase the NIR178 dose to 240mg BID or complete Part 3 with NIR178 160mg BID.			

6.3 Concomitant medications

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.

[redacted]

Prior antineoplastic therapies including medications, radiotherapy, and surgery are to be recorded on the separate Prior Antineoplastic Therapy eCRF during screening.

6.3.1 Permitted concomitant therapy

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

6.3.2 Permitted concomitant therapy requiring caution and/or action

NIR178 was demonstrated to be an inhibitor of CYP1A2 in vitro. Caffeine is a sensitive substrate of CYP1A2. Caution should be exercised if caffeine or caffeine containing food, beverages, or medications are consumed. Additionally, NIR178 was demonstrated to be a substrate of CYP1A2, therefore moderate and weak inhibitors of CYP1A2 should be used with caution.

NIR178 inhibited BCRP-mediated transport *in vitro*. Even though the risk of systemic inhibition of BCRP (e.g., liver, brain, and kidney) is predicted to be minimal to none, the potential risk of intestinal BCRP inhibition by NIR178 administered at clinically relevant doses cannot be ruled out. Therefore, concomitant administration of NIR178 with medications that are substrates of BCRP is permitted however caution should be exercised by the investigators (Table 14-2).

Anticoagulation is permitted if the patients are already at stable doses 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 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.

Please see Appendix 1 for further details.

6.3.3 Prohibited concomitant therapy

During the course of the study, patients must 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 following a documented discussion with Novartis. Such local therapies administrated during the study treatment must be listed on the Concomitant radiotherapy/surgery case report form (CRF) page. Additionally, other therapeutic monoclonal antibodies and immunosuppressive medications are prohibited.

GnRH therapy to maintain effective testosterone suppression levels is allowed for mCRPC patients.

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of an infusion reaction, irAEs, for prophylaxis against imaging contrast dye

[redacted]

allergy or replacement-dose steroids in the setting of adrenal insufficiency (providing this is ≤ 10 mg/day prednisone or equivalent), or transient exacerbations of other underlying diseases such as chronic obstructive pulmonary disease (COPD) requiring treatment for < 3 weeks. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next study drug administration. If more than 10 mg/day prednisone is used, study treatment should be suspended. Topical, inhaled, nasal and ophthalmic steroids are allowed.

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

As previously discussed, NIR178 was found to be an inhibitor and substrate of CYP1A2 in vitro. Therefore, strong inhibitors and moderate inducers of CYP1A2 as well as sensitive (except caffeine) and narrow therapeutic index substrates of CYP1A2 are prohibited.

Additionally, medications known to cause Torsades de pointes and prolong the QT interval are prohibited.

Please see Appendix 1 for further details.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each 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.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient was not randomized or did not start treatment.

For Japanese safety run-in part: Patients will be assigned by Novartis manually, outside IRT system.

6.4.2 Treatment assignment or randomization

Interactive Response Technology (IRT) will be used for treatment assignment, patient allocation and drug supply management for all patients.

In addition, in Part 2, patients will be randomized to one of the 3 treatment arms (Section 4.1 and Section 6.1) in a ratio of 1:1:1 through IRT.

[redacted]

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

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

For Japanese safety run-in part: Patients will be assigned by Novartis manually, outside IRT system. IRT will not be used for this part.

6.4.3 Treatment blinding

This is an open-label study.

6.5 Study drug preparation and dispensation

NIR178

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

PDR001

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.

6.5.1 Study treatment packaging and labeling

Study treatment, NIR178 and PDR001, will be provided as global clinical open-label patient specific supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

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.

NIR178 and PDR001 in different formulations and strengths can be used once they are approved.

[redacted]

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

For patients that are assigned by the IRT system, responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the patient.

6.5.2 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, the study treatment should be stored according to the instructions specified on the drug labels and in the [NIR178 (PBF-509) Investigator's Brochure] and [PDR001 Investigator's Brochure].

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

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

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

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

6.5.4 Disposal and destruction

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

[redacted]

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1, Table 7-2 and Table 7-3 lists all of the assessments and indicates with an "X", the visits when they are performed. Japanese safety run-in part will be conducted in accordance with Table 7-1. Part 3 visit schedule will be followed by the continuous BID visit schedule (Table 7-1).

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 evaluations must be performed ≤ 21 days of Cycle 1 Day 1 (except for the pregnancy test which must be performed within 72 hours before day 1 of every cycle and baseline imaging assessment which should be performed ≤ 28 days of Cycle 1 Day 1). 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 Cycle 1 Day 1. Laboratory and radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within the screening time window.

During the course of the study visits, tests and/or procedures should occur on schedule whenever possible. A visit window of +/- 3 days is allowed for assessments except Imaging and PK.

Imaging assessments have an on study visit window of ±1 week, regardless of dosing schedule or possible dose delays.

On PK collection days, the time windows are provided in Table 7-8 to Table 7-11. In situations when dosing is delayed, PK collections should also be delayed until the subsequent dose is given.

If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff/home nursing service to the patient's home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the patient to visit the site again.

[redacted]

Table 7-1 Visit evaluation schedule for patients in Part 1, Part 2 NIR178 S1 (NIR178 Schedule 1-BID continuous dosing), Part 3 and Japanese safety run-in

Visit Name	Category	Protocol Section	Screening	Cycle 1[c]						Cycle 2		Cycle 3		Day 1 of Subsequent cycles	End of study treatment (EoT)	Follow up *
Day of cycle				**1**	**2**	**8**	**15**	**22**	**28**	**1**	**15**	**1**	**15**			
Obtain Informed Consent	D	7.1.1.	X													
IRT Registration[a]	D	6.4, 7.1.1.1.	X													
Demography	D	7.1.1.3.	X													
Inclusion/exclusion criteria	D	5.2, 5.3.	X													
Medical History	D	7.1.1.3.	X													
Diagnosis and extent of cancer	D	7.1.1.3.	X													
Smoking History	D	7.1.1.3.	X													
Prior antineoplastic therapy	D	7.1.1.3.	X													
Prior/concomitant medications	D	7.1.1.3.	X	Throughout the study											X	X
Baseline tumor molecular characteristics	D	7.1.1.3.	X													
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5, 7.1.6, 7.1.7.													X	X
IRT Randomization[a]		6.4.	X												X	
Physical examination	S	7.2.2.1.	X	X			X			X	X (for Japanese safety run-in only)	X		X	X	
Performance status	D	7.2.2.4.	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	

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Visit Name	Category	Protocol Section	Screening	Cycle 1[c]						Cycle 2		Cycle 3		Day 1 of Subsequent cycles	End of study treatment (EoT)	Follow up *
Day of cycle				**1**	**2**	**8**	**15**	**22**	**28**	**1**	**15**	**1**	**15**			
Vital signs	D	7.2.2.2.	X	X			X			X	X	X	X	X	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	
Thyroid Panel (TSH, free T4, T3)	D	7.2.2.5.4.	X				X			X	X	X	X	X	X	
Coagulation (PTT/aPTT and PT or INR)	D	7.2.2.5.3.	X	If Clinically indicated												
Creatinine clearance	D	7.2.2.5.2.	X	X												
Hepatitis testing	D	7.2.2.5.5.	X													
HIV testing	D	7.2.2.5.5.	X													
Urinalysis (microscopic or macroscopic)	D	7.2.2.5.8.	X	If Clinically indicated												
Pregnancy test	D	7.2.2.5.7.	X	X						X		X		X	X	X
PSA (only for mCRPC patients)	D	7.2.2.5.8	X	X						X		X		X	X	
Disease assessment/Tumor evaluation per iRECIST, RECIST v 1.1 or Cheson et al (2014) for lymphoma, color photography of visible lesion(s) and PCWG3	D	7.2.1.	X									Every 8 weeks from C1D1 for 40 weeks and every 12 weeks thereafter until progression of disease per iRECIST or Cheson et al (2014) or patient withdrawal				X (If not performed within 30 days prior to EOT)	
Bone marrow biopsy or aspirate in patients with known bone marrow involvement (for Lymphoma only)	D	7.2.1.	X													
12 lead ECG	D	7.2.2.7.	X	X					X	X		X		X	X	
Adverse events	D	8.	X	Throughout the study											X	X
[redacted]																

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1[c]						Cycle 2		Cycle 3		Day 1 of Subsequent cycles	End of study treatment (EoT)	Follow up *
Day of cycle				**1**	**2**	**8**	**15**	**22**	**28**	**1**	**15**	**1**	**15**			
[redacted]																
NIR178 dosing	D	6.1.		As per assigned schedule												
PDR001 infusion	D	6.1.		X[a]						X		X		X		
PK sampling for NIR178, NJI765 and PDR001[b]	D	7.2.3.		X	X	X	X	X	X	X		X	X	X (up to cycle 6)	X	
Chest X-ray (For Japan only	D	7.2.2.6.	X				X				X					

*Please refer to Section 7.1.5 for safety follow up, Section 7.1.6 for disease progression follow up, Section 7.1.7 for survival follow up and Section 7.1.8 for information on lost to follow-up patients.
a: Not applicable for Japanese safety run-in; An optional tumor sample may also be collected at disease progression when patients continue on study treatment due to overall clinical benefit
b: Please refer to Section 7.2.3. for Japanese safety run-in;
c: Patients will be hospitalized during first cycle for Japanese safety run-in.

[redacted]

Table 7-2 Visit evaluation schedule for patients in Part 2 NIR178 S 2 (NIR178 Schedule 2 regimen-two weeks on two weeks off dosing)

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2		Cycle 3		Day 1 of Subsequent cycles	End of study treatment (EoT)	Follow up *
Day of cycle				**1**	**2**	**8**	**14**	**15**	**22**	**1**	**15**	**1**	**15**			
Obtain Informed Consent	D	7.1.1.	X													
IRT Registration	D	6.4, 7.1.1.1.	X													
Demography	D	7.1.1.3.	X													
Inclusion/exclusion criteria	D	5.2, 5.3.	X													
Medical History	D	7.1.1.3.	X													
Smoking history	D	7.1.1.3.	X													
Diagnosis and extent of cancer	D	7.1.1.3.	X													
Prior antineoplastic therapy	D	7.1.1.3.	X													
Prior/concomitant medications	D	7.1.1.3.	X	Throughout the study											X	X
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5, 7.1.6, 7.1.7.													X	X
IRT Randomization		6.4.	X												X	
Physical examination	S	7.2.2.1.	X	X				X		X		X		X	X	
Performance status	D	7.2.2.4.	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	
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	
Thyroid Panel (TSH, free T4, T3)	D	7.2.2.5.4.	X					X		X	X	X	X	X	X	
Coagulation (PTT/aPTT and PT or INR)	D	7.2.2.5.3.	X	If Clinically indicated												

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2		Cycle 3		Day 1 of Subsequent cycles	End of study treatment (EoT)	Follow up *
Day of cycle				**1**	**2**	**8**	**14**	**15**	**22**	**1**	**15**	**1**	**15**			
Creatinine clearance	D	7.2.2.5.2.	X	X												
Hepatitis testing	D	7.2.2.5.5.	X													
HIV testing	D	7.2.2.5.5.	X													
Urinalysis (microscopic or macroscopic)	D	7.2.2.5.8.	X	If Clinically indicated												
Pregnancy test	D	7.2.2.5.7.	X	X						X		X		X	X	X
Disease assessment/Tumor evaluation per iRECIST, RECIST v 1.1 or Cheson et al (2014) for lymphoma, color photography of visible lesion(s)	D	7.2.1.	X									Every 8 weeks from C1D1 for 40 weeks and every 12 weeks thereafter until progression of disease per iRECIST or Cheson et al (2014) or patient withdrawal				X (If not performed within 30 days prior to EOT)	
12 lead ECG	D	7.2.2.7.	X	X			X			X		X		X	X	
Adverse events	D	8.	X	Throughout the study											X	X
[redacted]																
NIR178 dosing	D	6.1.		As per assigned schedule												
PDR001 infusion	D	6.1.		X						X		X		X		

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2		Cycle 3		Day 1 of Subsequent cycles	End of study treatment (EoT)	Follow up *
Day of cycle				**1**	**2**	**8**	**14**	**15**	**22**	**1**	**15**	**1**	**15**			
PK sampling for NIR178, NJI765 and PDR001	D	7.2.3.		X	X	X	X	X	X	X		X	X	X (up to cycle 6)	X	

*Please refer to Section 7.1.5 for safety follow up, Section 7.1.6 for disease progression follow up, Section 7.1.7 for survival follow up and Section 7.1.8 for information on lost to follow-up patients.

a: An optional tumor sample may be collected at disease progression when patients continue on study treatment due to overall clinical benefit.

[redacted]

Table 7-3 Visit evaluation schedule for patients in Part 2 NIR178 S3 (NIR178 Schedule 3-one week on, one week of dosing)

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2		Cycle 3		Day 1 of Subsequent cycles	End of study treatment (EoT)	Follow up *
Day of cycle				**1**	**2**	**7**	**8**	**15**	**22**	**1**	**15**	**1**	**15**			
Obtain Informed Consent	D	7.1.1.	X													
IRT Registration	D	6.4, 7.1.1.1.	X													
Demography	D	7.1.1.3.	X													
Inclusion/exclusion criteria	D	5.2, 5.3.	X													
Medical History	D	7.1.1.3.	X													
Smoking history	D	7.1.1.3.														
Diagnosis and extent of cancer	D	7.1.1.3.	X													
Prior antineoplastic therapy	D	7.1.1.3.	X													
Prior/concomitant medications	D	7.1.1.3.	X	Throughout the study											X	X
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5, 7.1.6, 7.1.7.													X	X
IRT Randomization		6.4.	X												X	
Physical examination	S	7.2.2.1.	X	X				X		X		X		X	X	
Performance status	D	7.2.2.4.	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	
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	
Thyroid Panel (TSH, free T4, T3)	D	7.2.2.5.4.	X					X		X	X	X	X	X	X	
Coagulation (PTT/aPTT and PT or INR)	D	7.2.2.5.3.	X	If Clinically indicated												
Creatinine clearance	D	7.2.2.5.2.	X	X												

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2		Cycle 3		Day 1 of Subsequent cycles	End of study treatment (EoT)	Follow up *
Day of cycle				**1**	**2**	**7**	**8**	**15**	**22**	**1**	**15**	**1**	**15**			
Hepatitis testing	D	7.2.2.5.5.	X													
HIV testing	D	7.2.2.5.5.	X													
Urinalysis (microscopic or macroscopic)	D	7.2.2.5.8.	X	If Clinically indicated												
Pregnancy test	D	7.2.2.5.7.	X	X						X		X		X	X	X
Disease assessment/Tumor evaluation per iRECIST, RECIST v 1.1 or Cheson et al (2014) for lymphoma, color photography of visible lesion(s)	D	7.2.1.	X									Every 8 weeks from C1D1 for 40 weeks and every 12 weeks thereafter until progression of disease per iRECISTor Cheson et al (2014) or patient withdrawal			X (If not performed within 30 days prior to EOT)	
12 lead ECG	D	7.2.2.7.	X	X		X				X		X		X	X	
Adverse events	D	8.	X	Throughout the study											X	X
[redacted]																
NIR178 dosing	D	6.1.		As per assigned schedule												
PDR001 infusion	D	6.1.		X						X		X		X		

[redacted]

Visit Name	Category	Protocol Section	Screening	Cycle 1						Cycle 2		Cycle 3		Day 1 of Subsequent cycles	End of study treatment (EoT)	Follow up *
Day of cycle				**1**	**2**	**7**	**8**	**15**	**22**	**1**	**15**	**1**	**15**			
PK sampling for NIR178, NJI765 and PDR001	D	7.2.3.		X	X	X	X	X	X	X		X	X	X (up to cycle 6)	X	

*Please refer to Section 7.1.5 for safety follow up, Section 7.1.6 for disease progression follow up, Section 7.1.7 for survival follow up and Section 7.1.8 for information on lost to follow-up patients.

a: An optional tumor sample may be collected at disease progression when patients continue on study treatment due to overall clinical benefit.

[redacted]

7.1.1 Screening

The IRB/IEC study approved informed consent form (ICF) must be signed and dated before any study-specific screening procedure is performed. Procedures which are part of the clinical routine during the initial diagnostic work-up of the patient may be obtained before obtaining the ICF. A copy of the ICF must be given to the patient or to the person signing the form. The investigator or designee must record the date when the study informed consent was signed in the medical records of the patient.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 7-1, Table 7-2 and Table 7-3. Screening assessments must be completed within 21 days prior to the first dose of treatment except for the radiological tumor assessment which should be performed within 28 days prior to the first dose. Screening assessments must be repeated if outside of screening windows. Patients are allowed to re-screen after abnormal labs or symptoms are corrected or treated.

Submission of a newly obtained tumor sample (formalin fixed, in ethanol) is required from all patients (except for patients in Japanese safety run-in part) at screening, unless the patient has a recently obtained tumor sample that meets the following criteria (both criteria must be met):

- Biopsy sample was collected ≤ 6 months before 1st dose of study medication and the sample is available at the site.
- No immunotherapy was given to the patient since collection of biopsy sample.

For details refer to Section 7.2.4.

7.1.1.1 Eligibility screening

Following registering in the IRT (except for Japanese safety run-in patients) for screening, patient eligibility will be checked once all screening procedures are completed. Please refer and comply with detailed guidelines in the IRT manual.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment 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 Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

7.1.1.3 Patient demographics and other baseline characteristics

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

[redacted]

7.1.2 Treatment period

The treatment period commences on the first day of the first cycle of NIR178 and PDR001 combination.

During the study treatment period, patients will be regularly monitored to assess the safety and early anti-tumor activity of treatment. For purpose of scheduling and evaluations, a treatment cycle will consist of 28 days.

Patients who meet the following criteria **should continue treatment** in additional cycles:

- Patients who do not have a PD per iRECIST (Appendix 3) or Cheson et al 2014 (DLBCL), (and/or progressive disease per PCWG3 guidance (Appendix 5) for mCRPC).

Patients who meet the following criteria **might continue treatment** in additional cycles:

- Patients with confirmed PD per iRECIST (Appendix 3) or Cheson et al 2014 (DLBCL), (and/or progressive disease per PCWG3 guidance (Appendix 5) for mCRPC), if the Investigator considers it to be in the patient's best interest to remain on the study, and after documented discussion with the Novartis medical monitor.

Patients who meet the following criteria **will NOT continue treatment** in additional cycles:

- Patients who experience unacceptable toxicity.
- Rapid disease progression or threat to vital organs or critical anatomical sites [e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression] requiring urgent alternative medical intervention; significant, unacceptable or irreversible toxicities related to study treatment.
- Patients with confirmed PD per iRECIST (Appendix 3) or Cheson et al 2014 (DLBCL), (and/or progressive disease per PCWG3 guidance (Appendix 5) for mCRPC) unless they meet the criteria above for continuation of treatment. These patients will then enter the Safety follow-up period.
- Patients with an unconfirmed PD per iRECIST who show signs of clinical deterioration or toxicity. These patients will enter the Safety follow-up period, and will continue to be followed-up until confirmed irPD or initiation of a new treatment.

Clinical experience indicates that objective responses to immunotherapy follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while other target lesions are regressing ("mixed response") (Wolchok et al 2009). It is therefore reasonable to allow for these possibilities and continue to treat the patient until progression is confirmed and found to be advancing at the next imaging assessment as per iRECIST. An outline of the iRECIST is provided in Appendix 3.

These considerations should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the patient is not benefiting from study treatment and cannot be managed by the addition of supportive care.

[redacted]

During the treatment period, the patient is obliged to follow the investigators instructions with regards to contraception, concomitant medications and dosing regimen. There is no fixed duration; patients may continue treatment with the study drug until the development of an unacceptable toxicity that precludes any further treatment, disease progression, and /or treatment is discontinued at the discretion of the Investigator or by patient refusal. For details of assessments during the treatment period, refer to Table 7-1, Table 7-2 and Table 7-3.

7.1.3 Discontinuation of study treatment

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

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

Study treatment may be discontinued under the following circumstances:

- Adverse events
- Lost to follow-up
- Progressive disease as per confirmed iRECIST or Cheson et al (2014) (not as per RECIST v1.1); and/or as per PCWG3 guidance (Appendix 5) for mCRPC
  Patients may alternatively be re-treated following progression during dosing pauses
  Patients who progress on treatment should be discontinued unless they have a subsequent response in the absence of further treatment
- Physician's decision
- Study terminated by Novartis
- Patient/guardian decision
- Protocol deviation
- Technical problems
- Use of prohibited treatment. Refer to Appendix 1.
- Any other protocol deviation that results in a significant risk to the patient's safety
- Dose interruptions longer than specified in Section 6.3.1.

Patients must be discontinued if any of the following occur:

- Death
- Pregnancy

Patients who discontinue study/investigational treatment should undergo an end of study treatment visit and then be discontinued from the study treatment (please refer to Table 7-1, Table 7-2 and Table 7-3 for list of assessments to be performed). An End of Treatment Phase Disposition eCRF should be completed, giving the reason for stopping the study treatment. End of treatment/Premature withdrawal visit is not considered as the end of the study.

[redacted]

The investigator must also contact the IRT to register the patient's discontinuation from study treatment except for the Japanese run-in safety group.

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed every 8 weeks until documented disease progression, death, lost to follow-up, or withdrawal of consent.

Patients who transfer into another study or an alternative treatment option to continue provision of study treatment, will perform the end of treatment procedures (refer to Section 4.3).

7.1.4 Withdrawal of consent

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

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

In this situation, the investigator should make a reasonable effort (e.g. telephone, email, 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 subject are not allowed unless safety findings require communicating or follow-up.

All effort 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 data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

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

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

7.1.5 Follow up for safety evaluations

All patients receiving PDR001 must have safety evaluations for 150 days after the last dose of PDR001 or 30 days after the last dose of NIR178, whichever occurs later. The follow-up evaluations can be done either by telephone call or visit for the 30-, 90-, and 150-day safety follow-up visits.

[redacted]

Concomitant medications will be collected until the 30-day safety follow-up has been completed or the start of a new antineoplastic therapy, whichever occurs first. Adverse events should be captured on the appropriate eCRF for 150 days after the last dose of medication. If resolution of an adverse event continues past this timeframe, the investigator will still be responsible to undertake appropriate actions, but that information will not be entered into the clinical database. After initiation of a new post-treatment antineoplastic therapy, only AEs and SAEs suspected to be related to study treatment will be recorded in the Adverse Event CRF.

Data collected should be added to the Adverse Events CRF, the antineoplastic therapies since discontinuation of study treatment CRF, and the Concomitant Medications CRF. For female patients of child bearing potential, pregnancy tests will be performed as outlined in Section 7.2.2.5.7.

7.1.5.1 Follow- up period

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

7.1.6 Follow-up for disease progression

Patients who discontinue study treatment for any reason other than death, disease progression per confirmed iRECIST (Appendix 3) or Cheson et al (2014) for DLBCL and/or progressive disease per PCWG3 guidance (Appendix 5) for mCRPC while on treatment, clinical deterioration or clinical progression, lost to follow-up, consent withdrawal or study termination, also should return for tumor evaluation assessments every 8 weeks (+/- 7 days) during the first 40 weeks, and every 12 weeks (+/- 7 days) thereafter until disease progression, death, loss to follow-up or withdrawal of consent, whichever occurs first. Any newly started antineoplastic therapies during the follow-up period must be recorded on the Antineoplastic therapy since discontinuation eCRF. Once patient starts on new antineoplastic therapy post discontinuation of study treatment, patient does not need to be followed for disease progression.

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 eCRF should be completed.

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

7.1.7 Follow-up for survival

Upon completion of the 150-day safety follow-up or disease progression follow-up, all patients (except for those in Japanese safety run in) will be followed for survival via a phone call, email or letter, every 12 weeks until any of the following (whichever occurs first): death, withdrawal of consent, loss to follow-up or at least 24 months from the first dose of study treatment. Antineoplastic therapies or tumor directed surgical procedures initiated during the survival

[redacted]

follow-up period must be recorded on the Antineoplastic therapies since discontinuation of study drug eCRF.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, 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 three sets of criteria:

- RECIST v1.1 (Appendix 2)
- iRECIST (Appendix 3)
- Cheson et al (2014) criteria for lymphoma
- PCWG3 guidance (Appendix 5) for mCRPC

The local investigator's assessment will be used for the analysis of response according to RECIST v1.1 or Cheson et al (2014) criteria. For treatment decision making around study discontinuation due to progressive disease, iRECIST (for solid tumors) or confirmed progressive disease as per Cheson et al (2014) (for lymphoma) will be followed. For mCRPC, efficacy will be evaluated using RECIST 1.1, iRECIST and PCWG3 guidance (Appendix 5). In addition, imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The site manual provided by the designated imaging CRO will provide further details regarding image collection. During the course of the study, Novartis may decide to have a central review of the radiological assessments performed.

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

Any imaging assessments already completed during the routine work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images. The following assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or MRI
- Brain CT or MRI, if clinically indicated
- Whole body bone scan, if clinically indicated
- Localized bone CT, MRI or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI

[redacted]

- Color photography for any skin lesions present
- CT or MRI of other metastatic sites (e.g., neck), if clinically indicated

If a patient is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

If brain metastases are suspected at baseline, brain MRI or CT should be completed. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

If clinically indicated, a whole body bone scan should be performed per institutional standard of care (e.g., Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride (NaF) PET)). Localized CT, MRI or X-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI.

If clinically indicated, CT or MRI of other areas (e.g., neck) of disease as appropriate should be performed.

If skin lesions are present at screening, color photography should be acquired using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph.

At screening, lymphoma patients will undergo Fluorodeoxyglucose positron emission tomography (FDG-PET)CT scan and bone marrow biopsy if they have known bone marrow involvement. For patients with FDG avid tumors, all subsequent disease assessments will be performed with FDG-PET CT, using the 5-point scale (Cheson et al 2014). The avidity of up to six representative target lesions must be documented and the rest as non-target lesions. For patients with non-avid or variably FDG-avid tumors, CT scan with i.v. contrast of chest/abdomen/pelvis/additional known lesions will be performed. If at screening, a patient has a medical contraindication to CT i.v. contrast or develops a contraindication during the trial, the following radiologic assessments will be performed: a non-contrast chest CT and a contrast abdomen/pelvis Magnetic Resonance Imaging (MRI).

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Chest x-rays and ultrasound should not be used to measure tumor lesions.

Imaging assessments as described in Table 7-4 should be performed at the time points specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1, Table 7-2 and Table 7-3). Imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) during the first 40 weeks, and every 12 weeks (+/- 7 days) thereafter until disease progression, death, lost to follow-up or withdrawal of consent or patient starts new antineoplastic therapy post discontinuation of study treatment.

[redacted]

Imaging assessments should be scheduled using the randomization date as the reference date (not the date of the previous tumor assessment), and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Appendix 2).

If a patient has a PR or CR, the result will be confirmed by a new assessment after at least 4 weeks.

If a solid tumor patient has progressive disease, as per iRECIST, the result will be confirmed after at least 4 weeks.

Similarly, if a lymphoma patient has progressive disease, the result will be confirmed after at least 4 weeks per Cheson et al (2014) criteria.

For mCRPC, efficacy will be evaluated using RECIST 1.1, iRECIST and PCWG3 guidance (Appendix 5).

If possible, a single radiologist should perform all tumor response evaluations for an individual patient.

Any lesion that has been previously treated with radiotherapy should be considered as a non-target lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a target lesion.

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

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent or patient starts new antineoplastic therapy post discontinuation of study treatment, tumor assessments must continue to be performed every 8 weeks until documented disease progression, death, lost to follow-up, or withdrawal of consent.

[redacted]

Table 7-4 Imaging/Disease Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI(with intravenous contrast enhancement)	Mandated	Mandated, every 8 weeks during the first 40 weeks, and every 12 weeks (+/- 7 days) thereafter
Brain CT or MRI	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Whole body bone scan	Mandatory for patients with mCRPC. If clinically indicated for all other indications	For patients with mCRPC: Mandated, every 8 weeks (+/- 7 days) for the first 40 weeks, and every 12 weeks (+/- 7 days) thereafter until disease progression, study treatment discontinuation**, or start of new antineoplastic therapy. If clinically indicated for all other indications
Bone marrow biopsy or aspirate (for lymphoma patients)*	Mandatory at screening	To confirm complete responses (CR), in patients with bone marrow involvement prior to study treatment
FDG-PET/CT	For lymphoma patients with known bone marrow involvement and/or FDG-avid tumors	All subsequent disease assessments; every 8 weeks during the first 40 weeks, and every 12 weeks (+/- 7 days) thereafter for patients with FDG-avid tumors
Localized bone CT, MRI or x-ray (e.g. neck, bone, prostate or prostate bed)	For any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Color photography (with scale/ruler)	For any skin lesions present	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
CT or MRI of other metastatic sites (e.g., neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
*- Documentation of status of bone marrow involvement by lymphoma based on prior bone marrow biopsy or aspirate findings is required at screening for all patients. If no such documentation is available then a bone marrow biopsy or aspirate should be performed at screening. ** Perform scan at EOT if a scan was not conducted within the 30 days prior to EOT.		

7.2.2 Safety and tolerability assessments

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

[redacted]

During the COVID-19 pandemic that limits or prevents on-site study visits, regular phone or virtual calls will occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the patient's health status until the patient can again visit the site.

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed as indicated in Table 7-1, Table 7-2 and Table 7-3.

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

For Japan only: oxygen saturation (SpO2) will be measured by pulse oximetry for Japanese patients every time physical examination is performed as indicated in Table 7-1. The results of SpO2 will be recorded only in the source documentation.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before infusion and as indicated in Table 7-1, Table 7-2 and Table 7-3 as per institutional standards. Vital signs should be assessed in the same position through the study. These assessments will be mandatory while patients are receiving study medications.

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 will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1, Table 7-2 and Table 7-3.

7.2.2.4 Performance status

ECOG Performance status scale will be used as described in the Table 7-5 and should be assessed as indicated in Table 7-1, Table 7-2 and Table 7-3.

[redacted]

Table 7-5 ECOG performance status

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

Note: Grade 5 (death) was removed from this table. This information will be collected on a separate eCRF.

7.2.2.5 Laboratory evaluations

Sites will use their local laboratories for the analysis of all safety lab samples collected at the time points indicated in Table 7-1, Table 7-2, Table 7-3 and Table 7-6. More frequent assessments may be performed if clinically indicated, or at the investigator's discretion and these should be recorded on the Unscheduled Visit eCRFs.

Screening examinations performed ≤72 hours prior to day 1 cycle 1, do not need to be repeated prior to dosing for Cycle 1, Day 1.

Abnormal laboratory values that are clinically significant (e.g., require an interruption or delay of study treatment, lead to clinical symptoms, or require therapeutic intervention) must be documented in the Adverse Event eCRF.

Novartis will be provided with a copy of the site's local laboratory certification and tabulation of the normal ranges for each parameter required at study start and should be kept up to date on an ongoing basis. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

[redacted]

Table 7-6 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN) or Urea, Uric Acid Amylase, Lipase, Glucose (non-fasting)
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, pH, Protein, Specific Gravity)
Coagulation	Prothrombin time (PT), International normalized ratio [INR]), Partial thromboplastin time (PTT) or Activated partial thromboplastin time (aPTT)
Thyroid	T3 [free], T4 [free], TSH
Virology panel	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR (baseline), HIV
Pregnancy Test	If the patient is a woman of child-bearing potential,a serum pregnancy test should be performed at screening, monthly during the study, and at the end of treatment. A serum or urine pregnancy test should be performed monthly during the safety follow-up period.

[redacted]

7.2.2.5.1 Hematology

Hematology tests are to be performed as outlined in Table 7-6 by the local laboratory according to the visit schedule outlined in Table 7-1, Table 7-2, and Table 7-3.

7.2.2.5.2 Clinical chemistry

Clinical chemistry tests are to be performed as outlined in Table 7-6 by the local laboratory according to the visit schedule outlined in Table 7-1, Table 7-2, and Table 7-3. It should be noted in the patient's eCRF if the patient was fasting at the time of blood sampling.

7.2.2.5.3 Coagulation

Coagulation will be measured/calculated at screening. The schedule is outlined in Table 7-1, Table 7-2, Table 7-3 and Table 7-6.

7.2.2.5.4 Thyroid function

A full panel for thyroid function is required at screening (TSH, T3 [free] and T4 [free]). At other visits, only TSH is required unless the results are abnormal or it is increasing to an extent deemed clinically significant. Testing is to be performed as outlined in Table 7-6 by the local laboratory according to the visit schedule outlined in Table 7-1, Table 7-2, and Table 7-3.

7.2.2.5.5 Virology panel

Virology panel outlined in Table 7-6 will be performed as per the assessment schedule in Table 7-1, Table 7-2 and Table 7-3.

[redacted]

7.2.2.5.6 Serology panel

Serology testing may be done on remnant serum samples if a patient experiences an adverse event. The testing will be conducted by a central lab.

7.2.2.5.7 Pregnancy and assessments of fertility

A serum pregnancy test must be performed at screening, every month during the study and at the end of treatment visit. If the screening pregnancy test is performed within 72 hours of cycle 1 day 1, pregnancy test does not have to be repeated.

Every month during the safety follow-up period and at the end of the safety follow-up period, a serum or urine pregnancy test must be performed. 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.

A pregnancy test is only needed if the patient is a woman of child-bearing potential.

During the COVID-19 pandemic, if the patient cannot visit the site to have serum pregnancy tests done, locally available urine pregnancy test kits may be used. Relevant patients can perform the urine pregnancy test at home and report the result to the site. It is important that patients are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the patient so that the Site is informed of the pregnancy test results.

7.2.2.5.8 Urinalysis

Dipstick measurements for specific gravity, pH, protein, glucose and blood will be performed as outlined in Table 7-6 and as indicated in Table 7-1, Table 7-2 and Table 7-3. Any significant findings on dipstick will be followed up with a microscopic evaluation where Microscopic Panel (Red Blood Cells, White Blood Cells, Bacteria, and Epithelial cells will also be measured).

[redacted]

7.2.2.6 [For Japan only] Radiological examinations

7.2.2.6.1 Chest X-ray

A 2-view chest X-ray will be performed as outlined in Table 7-1, Table 7-2 and Table 7-3.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

All ECG evaluations will be independently reviewed at central labs. Instructions for the collection and transmission of ECGs to the central ECG laboratory will be provided in the ECG Manual. A standard 12-lead ECG will be performed as per the assessment schedule in [redacted] t the same time point

should be taken after the ECGs are completed. The ECGs must be performed in triplicate, at least 1-2 minutes apart, as shown in the tables below.

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

Table 7-7 Central ECG collection plan

Cycle	Day	Time	ECG Type
Screening	-21 to -1 days	Anytime during the screening period	12 Lead, triplicate
1	1	Pre-dose (baseline ECG) 2-hr post-NIR178 dose, ± 15 min	12 Lead, triplicate
1	7 (only required for Part 2 NIR178 Schedule 3)	Pre-dose 30 min, 1-hr, 2-hr, 3-hr, 4-hr post-NIR178 dose, ± 15 min	12 Lead, triplicate
1	14 (only required for Part 2, NIR178 Schedule 2)	Pre-dose 30 min, 1-hr, 2-hr, 3-hr, 4-hr post-NIR178 dose, ± 15 min	12 Lead, triplicate
1	28 (only required for Part 1 and Part 2 NIR178 Schedule 1)	Pre-dose 2-hr post-NIR178 dose, ± 15 min	12 Lead, triplicate
2 to 6	1	Pre-dose	12 Lead, triplicate
EOT	1	Any time	12 Lead, triplicate
Unscheduled	N/A	Any time	12 Lead, triplicate

7.2.3 Pharmacokinetics and immunogenicity assessments

Serial blood samples will be collected at specified time points as outlined in in Table 7-8, Table 7-9, Table 7-10 and Table 7-11 to measure NIR178 and its metabolite, NJI765, PDR001 and anti-drug antibodies (ADAs). Blood samples should be collected from the arm oppositefrom the study drug infusion, or from another site. Complete instructions for sample processing, handling and shipment will be provided in the [CNIR178X2201 Laboratory Manual].

PK and anti-drug antibody samples will also be collected at the End of Treatment Visit and in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or if anti-drug antibody is suspected, at which time those samples could be used to measure any relevant biomarkers, to understand the infusion reaction/adverse event better.

The exact date and clock times of study drug administration and blood sample collection will be recorded on the appropriate electronic care report form (eCRF). Any sampling issues should be noted on the eCRF and on appropriate source documentation. If vomiting occurs within 4

[redacted]

hours following NIR178 oral administration on dosing days with a pre- and post-dose PK blood collection, the clock time of vomiting should be recorded in the Dose Administration Record (DAR) PK eCRF page. For PDR001, in case the administration is stopped or temporarily paused during infusion, these events should be captured in the appropriate DAR PK eCRF page.

Residual PK and ADA serum or plasma samples used for PK and/or ADA analysis may also be used for exploratory PK and/or PD analyses.

During the COVID-19 pandemic that limits or prevents on-site study visits, or if visits by site staff to a patient's home are not feasible the collection of samples may be modified by Novartis and will be communicated to the Investigator.

Table 7-8 Pharmacokinetic blood collection log for PDR001 and ADA (all study parts and schedules, including Japanese safety run-in and Part 3)

Cycle	Study day	Scheduled time point (Sampling window)	Analytes
1 (Cycle 2 for Japanese safety run-in patients) [e]	1	Pre-dose [b] (0 h)	PDR001 and ADA [a]
1 (Cycle 2 for Japanese safety run-in patients) [e]	1	1 h (± 5 min) post end of C1D1 infusion dose [c]	PDR001
1 (Cycle 2 for Japanese safety run-in patients) [e]	8	168 h (± 8 hr) post dose	PDR001
1 (Cycle 2 for Japanese safety run-in patients) [e]	15	336 h (± 8 hr) post dose	PDR001
1 (Cycle 2 for Japanese safety run-in patients) [e]	22	504 h (± 8 hr) post dose	PDR001
2	1	Pre-dose [b] of cycle 2 (0 h)	PDR001 and ADA [a]
3	1	Pre-dose [b] of cycle 3 (0 hr)	PDR001 and ADA [a]
3	1	1 hr (± 5 min) post end of C3D1 infusion dose [c]	PDR001
3	15	336 hr (± 8 hr) post dose	PDR001
4	1	Pre-dose [b] of cycle 4 (0 h)	PDR001 and ADA [a]
5	1	Pre-dose [b] of cycle 5 (0 h)	PDR001 and ADA [a]
6	1	Pre-dose [b] of cycle 6 (0 h)	PDR001 and ADA [a]
EOT [d]		Anytime	PDR001 and ADA [a]
Unscheduled		Anytime	PDR001 and ADA [a]

[redacted]

Cycle	Study day	Scheduled time point (Sampling window)	Analytes
Blood 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. [a] Immunogenicity (IG) (Anti-Drug [PDR001] Antibody): blood samples to be collected for anti-drug antibody together with PK samples [b] Pre-dose blood samples should be collected prior to start of infusion of any treatment [c] PDR001 sampling time is relative to the end of PDR001 infusion [d] A PK sample collection will occur at cycle 6 or EOT, whichever occurs first Note: For Japanese safety run-in, PDR001 samples collection will begin from cycle 2 onwards. [e] As of protocol amendment 6, patients enrolled in the Japanese safety run-in part will receive NIR178 in combination with PDR001 starting at Cycle 1 and PDR001/ADA PK sample collections will begin at Cycle 1			

Table 7-9 Pharmacokinetic blood collection log for NIR178: Part 1, Part 2, Part 3 (NIR178 Schedule 1), and Japanese safety run-in

Cycle	Day	Scheduled Time Point (h)	Analyte [b]
1	1	Pre-dose (0 h)	NIR178 and NJI765
1	1	15 min post-dose (± 5 min)	NIR178 and NJI765
1	1	30 min post-dose (± 5 min)	NIR178 and NJI765
1	1	1 h post-dose (± 5 min)	NIR178 and NJI765
1	1	1.5 h post-dose (± 5 min)	NIR178 and NJI765
1	1	2 h post dose (± 10 min)	NIR178 and NJI765
1	1	3 h post-dose (± 10 min)	NIR178 and NJI765
1	1	4 h post-dose (± 30 min)	NIR178 and NJI765
1	1	8 h post-dose (± 30 min)	NIR178 and NJI765
1	2	Pre-dose (0hr/12 hrs post day 1 evening dose)	NIR178 and NJI765
1	8	Pre-dose (0 h)	NIR178 and NJI765
1	15	Pre-dose (0 h)	NIR178 and NJI765
1	28	Pre-dose (0 h)	NIR178 and NJI765
1	28	15 min post-dose (± 5 min)	NIR178 and NJI765
1	28	30 min post-dose (± 5 min)	NIR178 and NJI765
1	28	1 h post-dose (± 5 min)	NIR178 and NJI765
1	28	1.5 h post-dose (± 5 min)	NIR178 and NJI765
1	28	2 h post dose (± 10 min)	NIR178 and NJI765
1	28	3 h post-dose (± 10 min)	NIR178 and NJI765
1	28	4 h post-dose (± 30 min)	NIR178 and NJI765
1	28	8 h post-dose (± 30 min)	NIR178 and NJI765
2	1	Pre-dose (0hr/12 hrs post day 28 evening dose)	NIR178 and NJI765
3	1	Pre-dose	NIR178 and NJI765
4	1	Pre-dose	NIR178 and NJI765
5	1	Pre-dose	NIR178 and NJI765
6	1	Pre-dose	NIR178 and NJI765
EOT [a]		Anytime	NIR178 and NJI765
Unscheduled		Anytime	NIR178 and NJI765
[a] a PK sample collection will occur at cycle 6 or EOT, whichever occurs first [b] Same blood samples collected to assess PK of NIR178 will be used to measure its metabolite NJI765 as both analytes are assayed simultaneously by the analytical laboratory.			

[redacted]

Table 7-10 Pharmacokinetic blood collection log for NIR178 Part 2 (NIR178 Schedule 2)

Cycle	Day	Scheduled Time Point (h)	Analyte [b]
1	1	Pre-dose (0 h)	NIR178 and NJI765
1	1	15 min post-dose (± 5 min)	NIR178 and NJI765
1	1	30 min post-dose (± 5 min)	NIR178 and NJI765
1	1	1 h post-dose (± 5 min)	NIR178 and NJI765
1	1	1.5 h post-dose (± 5 min)	NIR178 and NJI765
1	1	2 h post dose (± 10 min)	NIR178 and NJI765
1	1	3 h post-dose (± 10 min)	NIR178 and NJI765
1	1	4 h post-dose (± 30 min)	NIR178 and NJI765
1	1	8 h post-dose (± 30 min)	NIR178 and NJI765
1	2	Pre-dose (0hr/ 12 hrs post day 1 evening dose)	NIR178 and NJI765
1	14	Pre-dose (0 h)	NIR178 and NJI765
1	14	15 min post-dose (± 5 min)	NIR178 and NJI765
1	14	30 min post-dose (± 5 min)	NIR178 and NJI765
1	14	1 h post-dose (± 5 min)	NIR178 and NJI765
1	14	1.5 h post-dose (± 5 min)	NIR178 and NJI765
1	14	2 h post dose (± 10 min)	NIR178 and NJI765
1	14	3 h post-dose (± 10 min)	NIR178 and NJI765
1	14	4 h post-dose (± 30 min)	NIR178 and NJI765
1	14	8 h post-dose (± 30 min)	NIR178 and NJI765
1	15	12 hrs post day 14 evening dose	NIR178 and NJI765
EOT [a]		Anytime	NIR178 and NJI765
Unscheduled		Anytime	NIR178 and NJI765

[a] a PK sample collection will occur at cycle 6 or EOT, whichever occurs first

[b] Same blood samples collected to assess PK of NIR178 will be used to measure its metabolite NJI765 as both analytes are assayed simultaneously by the analytical laboratory.

[redacted]

Table 7-11 Pharmacokinetic blood collection log for NIR178 Part 2 (NIR178 Schedule 3)

Cycle	Day	Scheduled Time Point (h)	Analyte [b]
1	1	Pre-dose (0 h)	NIR178 and NJI765
1	1	15 min post-dose (± 5 min)	NIR178 and NJI765
1	1	30 min post-dose (± 5 min)	NIR178 and NJI765
1	1	1 h post-dose (± 5 min)	NIR178 and NJI765
1	1	1.5 h post-dose (± 5 min)	NIR178 and NJI765
1	1	2 h post dose (± 10 min)	NIR178 and NJI765
1	1	3 h post-dose (± 10 min)	NIR178 and NJI765
1	1	4 h post-dose (± 30 min)	NIR178 and NJI765
1	1	8 h post-dose (± 30 min)	NIR178 and NJI765
1	2	Pre-dose (0hr/12 hrs post day 1evening dose)	NIR178 and NJI765
1	7	Pre-dose (0 h)	NIR178 and NJI765
1	7	15 min post-dose (± 5 min)	NIR178 and NJI765
1	7	30 min post-dose (± 5 min)	NIR178 and NJI765
1	7	1 h post-dose (± 5 min)	NIR178 and NJI765
1	7	1.5 h post-dose (± 5 min)	NIR178 and NJI765
1	7	2 h post dose (± 10 min)	NIR178 and NJI765
1	7	3 h post-dose (± 10 min)	NIR178 and NJI765
1	7	4 h post-dose (± 30 min)	NIR178 and NJI765
1	7	8 h post-dose (± 30 min)	NIR178 and NJI765
1	8	12 hrs post day 7 evening dose	NIR178 and NJI765
EOT [a]		Anytime	NIR178 and NJI765
Unscheduled		Anytime	NIR178 and NJI765

[a] a PK sample collection will occur at cycle 6 or EOT, whichever occurs first

[b] Same blood samples collected to assess PK of NIR178 will be used to measure its metabolite NJI765 as both analytes are assayed simultaneously by the analytical laboratory.

7.2.3.1 Analytical methods

Concentrations of NIR178 and NJI765 will be determined from incurred plasma samples using a validated LC/MS-MS assay with a lower limit of quantification (LLOQ) of 1.00 ng/mL or lower for both analytes. The quantification of these two analytes for PK characterization will occur simultaneously at a Novartis' designated analytical laboratory and hence does not require collection of a separate blood sample series for each.

Concentrations of PDR001 will be determined from serum using a validated LC/MS-MS assay.

Anti-PDR001 antibodies will be determined from serum using validated homogenous ELISA.

[redacted]

[redacted]

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

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

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 150 days following the last dose of PDR001 or 30 days after the last dose NIR178, whichever occurs later. After initiation of new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected in the Adverse Event 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 and graded 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, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected though 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 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. 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
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)

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

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

[redacted]

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST 1.1 or iRECIST criteria for solid tumors or as per Cheson et al (2014) guidelines for hematological malignancies), 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.

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,

[redacted]

- 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

8.2.2 Reporting

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 last dose of PDR001, or 30 days after the last dose of NIR178, whichever occurs later, 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.

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

Any SAEs experienced after the 150 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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

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

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

[redacted]

the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis 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 study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study and the newborn will be followed up to 12 months after delivery date. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

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

8.6 Data Monitoring Committee

An independent data monitoring committee will not be formed for this exploratory phase II study. Individual patient data will be reviewed on an ongoing basis and aggregate safety data and the primary endpoint will be monitored on ongoing basis 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 (see Section 10.7) at the respective time.

[redacted]

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).

[redacted]

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

9.3 Data collection

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

9.4 Database management and quality control

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

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

[redacted]

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

For EDC studies, after database lock, the investigator will receive 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. Data will be summarized using descriptive statistics (continuous data) and/or contingency table (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements and all relevant PK and PD measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The study data will be analyzed and reported based on all patients' data up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. Any additional data for patients continuing to receive study treatment past the data cutoff date for the primary Clinical Study Report, as allowed by the protocol, will be reported at completion of the study as defined in Section 4.3.

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

- Part 1: All summaries, listings and figures will be presented by tumor type.
- Part 2: All summaries, listings and figures will be presented by treatment groups.
- Part 3: All summaries, listings and figures will be presented by tumor type and treatment group.

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 CSR as separate listings.

The data from patients in Japanese safety run-in part will be reported in the CSR separately from the Phase II part of the data regardless of whether Japanese patients will participate the Phase II part of the study.

10.1 Analysis sets

10.1.1 Full Analysis Set

For Part 1, Part 3 and Japanese safety run-in part of the study, the Full Analysis Set (FAS) comprises all patients who received at least one full or partial dose of assigned combination of study drugs. Patients will be analyzed according to the planned treatment.

[redacted]

For Part 2 of the study: the Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

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 NIR178 or PDR001. 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 Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PAS) includes all patients who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives one of the planned treatments
- Subject provides at least one PK parameter
- Subject did not vomit within 4 hours after the dosing of NIR178

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by tumor type for the FAS.

Relevant medical histories and current medical at baseline will be summarized by system organ class and preferred term, by tumor type.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below.

The duration of exposure in months for NIR178 and PDR001 as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

The duration of exposure will also be presented for the study treatment.

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

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

10.4 Primary objective

There are three parts to the study. The primary objective for Part 1 is to evaluate the efficacy of NIR178 in combination to PDR001 in patients with selected advanced solid tumors and DLBCL.

The primary objective for Part 2 is to assess several continuous and intermittent dosing schedule of NIR178 in combination with PDR001 in NSCLC.

The primary objective for Part 3 is to further evaluate the efficacy of intermittent or continuous dosing schedules (if selected) of NIR178 in combination with PDR001 in one or two selected tumor types based on the emerging data from part 1 and part 2.

10.4.1 Variable

The variable used to evaluate the primary objective is overall response rate (ORR), defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR), as per local review and according to RECIST v1.1 (Refer to Appendix 2 for solid tumors and Cheson et al (2014) for DLBCL).

10.4.2 Statistical hypothesis, model, and method of analysis

Part 1:

This part will contain thirteen groups: DLBCL at NIR178 160 mg BID, pancreatic cancer at NIR178 160 mg BID, HNSCC IO naive at NIR178 160 mg BID, urothelial cancer at NIR178 160 mg BID, RCC IO naive at NIR178 160 mg BID, TNBC at NIR178 160 mg BID, melanoma IO pretreated NIR178 160 mg BID, HNSCC IO pretreated NIR178 160 mg BID, MSS CRC RAS wildtype NIR178 160 mg BID, MSS CRC RAS mutant NIR178 160 mg BID, RCC IO pretreated at NIR178 240 mg BID, RCC IO naive at NIR178 240 mg BID, and mCPRC at NIR178 240 mg BID. All doses are given in combination with PDR001 400 mg Q4W. An adaptive Bayesian design (Neuenschwander et al 2016) will be used to assess activity of treatment in terms of overall response rate (ORR) within tumor type and across each tumor types.

The efficacy data from the Non-HNSCC patients, MSS CRC patients with unknown RAS status and IO naive melanoma patients will not be included in the statistical model. The design of the trial adapts to the data that are accumulated in the trial in such a way as to accommodate three possibilities:

- Scenario A: ORR is similar across tumor types
- Scenario B: ORR is similar for some tumor types and different in others
- Scenario C: The various tumor types have distinct ORR

[redacted]

The pre-specified analysis is adaptive in the sense that when response is similar across tumor types (Scenario A), then it borrows from across the various tumor types. In case some of the tumor types have similar ORR (Scenario B), the model provide more precise estimate of ORR rates for those tumor types with similar response rates by allowing borrowing only across these tumor types. In the other possibility (the various tumor types have distinct anti-tumor activity (Scenario C)); the design allows little/no borrowing across tumor types. In this case the trial will be similar to traditional stratified analysis.

A hierarchical model (HM) will be used to analyze the binary data to facilitate the borrowing as specified above. Response rates (π_j) will be inferred for tumor group j (= 1,…,13). For each tumor type j, the number of responders follows a binomial distribution;

$$r_j \sim \text{Bin}\,(n_j, \pi_j)$$

We further let the parameters $\theta j = \log\,(\pi_j / (1 - \pi_j))$ (logistic transformation) be either exchangeable with some of the tumor types, or non-exchangeable with any of them. Based on the number of strata in this trial, we allow for two exchangeability distributions, which, for example, accounts for the case where some tumor type show no efficacy and some are promising. Thus, for each tumor type j, three possibilities arise, with respective probabilities $p_j = (\, p_{j1}, p_{j2}, p_{j3}\,)$, as follows:

1. With probability p_{j1} (probability group j belongs to exchangeability set 1) the parameter θj follows a normal distribution with exchangeability parameters μ_1 and τ_1:

$$\theta j \sim N(\mu_1, \tau_1^2)$$

2. With probability p_{j2} (probability group j belongs to exchangeability set 2) θj follows a normal distribution with exchangeability parameters $\mu_1 < \mu_2$ and τ_2:

$$\theta j \sim N(\mu_2, \tau_2^2)$$

3. With remaining probability $p_{j3} = 1 - p_{j1} - p_{j2}$ (probability group j is not exchangeable with any other group), θj follows a weakly-informative prior distribution

$$\theta_j \sim N(m_w, v_w)$$

For the detailed specifications of m_w, v_w, the a-priori weights p_j (j=1,⋯,J), and the prior distributions for μ_1, τ_1, μ_2, and τ_2, see (Appendix 4). At any given time of the trial, including at the end, posterior probabilities of the various parameters will be estimated using Markov chain Monte Carlo methods.

The results at the final analysis within a tumor type will be regarded to be positive if both of the following conditions are met:

a. posterior mean ≥ "clinically meaningful activity" threshold (column for C2 in Table 10-1) (i.e. posterior mean ORR >= C2)
b. Posterior probability of "not being clinically meaningful" (column for C1 in Table 10-1) is less than 10% (i.e., prob(ORR <= C1|data) < 10%)

[redacted]

Table 10-1 Type of tumors of interest with definition of being clinically meaningful

Disease Code	Tumor type	Not Clinically meaningful (C_1)	Clinically meaningful (C_2)
T1	DLBCL[a]	<= 10%	>= 20%
T2	Pancreatic[b]	<= 8%	>= 16%
T3	HNSCC naive[c]	<= 13%	>= 23%
T4	Urothelial[d]	<= 15%	>= 27%
T5	RCC naive at 160 mg	<= 25%	>= 37%
T6	TNBC[g]	<= 5%	>= 13%
T7	Melanoma pretreated[h]	<= 10%	>= 25%
T8	HNSCC pretreated	<= 5%	>= 13%
T9	MSS CRC – RAS wildtype[f]	<= 5%	>= 13%
T10	MSS CRC – RAS mutant[f]	<= 5%	>= 13%
T11	RCC pretreated at 240 mg	<= 10%	>= 20%
T12	RCC naive at 240 mg	<= 25%	>= 37%
T13	mCRPC at 240 mg	<= 10%	>= 35%

Interim analysis will be done when at least 10 patients in any indication have at least one post-baseline assessment (except for MSS-CRC and RCC naive at 240 mg patients i.e. T9, T10and T12, no interim analysis will be done).

Extend recruitment of up to 30 patients in each tumor type according to IA outcome [P(clinically meaningful) > 20%].

a. Ansell et al (2009) b. Kunk et al (2016) c. Fuereder (2016) d. Rosenberg et al (2016).
e. Motzer et al (2015) f. Le et al (2015) g. Goodman (2015) h. Hodi et al (2016). i. Bendell et al (2019)

Part 2:

Different schedules of NIR178 in combination with PDR001 in NSCLC will be evaluated by using the efficacy, safety and tolerability data. For details of safety analysis, please refer to Section 10.5.2.

Primary endpoint for efficacy analysis is ORR. The analysis is described as follows:

Overall response rate (ORR) will be provided for each schedule along with corresponding 90% confidence interval (CI). The prior distribution of ORR will be a minimally informative unimodal beta distribution with parameter a = 1/3 and b = 1 (note: this assumes a priori response rate of 25%). Posterior summaries for ORR (including 90% credible intervals and probability of ORR to fall in the activity interval defined below) will be provided.

[0, 20%): No improvement of ORR

[20%, 33%): Limited improvement of ORR

[33%, 100%]: Clinically meaningful improvement of ORR

The difference between the ORR in different schedules will be summarized.

[redacted]

For Part 2 of the study, the probability that one schedule is greater than another schedule given the data will be provided, i.e.

i. Posterior probability that ORR for schedule 1 is greater than schedule 2
ii. Posterior probability that ORR for schedule 2 is greater than schedule 3.
iii. Posterior probability that ORR for schedule 1 is greater than schedule 3.

In addition, posterior probability that ORR for one schedule is greater than the other two schedules will also be provided.

The posterior mean of the differences of ORR between the schedules and the corresponding 90% credible intervals will also be provided.

Part 3:

As of protocol amendment 6, Part 3 will explore the safety, efficacy and pharmacokinetics of the FCT formulation of NIR178 continuous dosing in combination with PDR001. TNBC is one of the selected tumor groups in Part 3. However, the TNBC patients in Part 3 will be analyzed by treatment group, separately from Part 1 TNBC patients since the inclusion/exclusion criteria are different and the patients in Part 3 will receive FCT formulation. ORR data will be analyzed similarly as done for Part 1. The efficacy intervals for the TNBC group will be the same as reported in Table 10-1 for the TNBC group. A second tumor group may be considered for Part 3 after completion of Part 1.

ORR will be provided for TNBC in Part 3 along with corresponding 90% confidence interval (CI). The prior distribution of ORR will be a minimally informative unimodal beta distribution with parameter a = 0.176 and b = 1 (note: this assumes a priori response rate of 15%). Posterior summaries for ORR (including 90% credible intervals and probability of ORR to fall in the activity interval defined below) will be provided.

[0, 5%): No improvement of ORR

[5%, 13%): Limited improvement of ORR

[13%, 100%]: Clinically meaningful improvement of ORR

10.4.3 Handling of missing values/censoring/ discontinuations

At final analysis, confirmed partial or complete responses reported prior to any additional anticancer therapy will be considered as responses in the calculation of ORR irrespective of the number of missed assessments before response.

At interim analyses, patients are considered to be evaluable if they are ongoing with study treatment and have at least one post-baseline response assessment, or who have discontinued study treatment. This total will be used for percentage calculation of ORR. For the purpose of the IA, if a patient is still on study and the last available efficacy assessment is a PR/CR which is yet to be confirmed by a subsequent scan, then this patient will be considered as a responder.

For solid tumor, patients with a best overall response of ‘Unknown’ or ‘Not Assessed’ per RECIST v1.1 will be considered as non-responders and will be included in the denominator in estimating the ORR. For lymphoma, patients with unknown or missing response or who are

[redacted]

treated in the study but provide no information on response at the end of treatment will be treated as non-responders and will be included in the denominator when calculating ORR.

[redacted]

10.5 Secondary objectives

10.5.1 Efficacy objectives

The secondary objective is to assess the efficacy of NIR178 in combination of PDR001 with respect to ORR (using iRECIST), disease control rate (DCR), duration of response (DOR), progression free survival (PFS) and overall survival (OS) by RECIST v1.1 and iRECIST (for solid tumors), also as per PCWG3 guidance (Appendix 5) for mCRPC, and Cheson et al (2014) (for DLBCL).

ORR: Overall response rate (ORR) as per iRECIST will be provided for each tumor type along with corresponding 90% confidence interval (CI).

DCR: DCR will be summarized by tumor type with accompanying 95% confidence intervals.

DOR, PFS and OS: DOR, PFS and OS will be presented descriptively using Kaplan-Meier plots by tumor types and treatment groups. In addition, the median DOR and corresponding 90% confidence interval will be presented. PFS and OS distributions will be summarized by tumor type presenting the median PFS and OS time with accompanying 90% confidence intervals along with Kaplan-Meier estimates for PFS and OS at 4, 6, 9, 12, 18 and 24 months. More details will be provided in the SAP.

For mCRPC patients, PSA at each time-point will be listed and change from baseline in PSA may be plotted and summarized if there are sufficient patients. More details will be provided in the SAP.

All efficacy data from the patients from Japanese safety run-in part will be listed separately. These patients will not be summarized with the other patients.

All efficacy data from the non-HNSCC patients and IO naive melanoma patients will be listed separately and will not be summarized with the other patients. All efficacy data from patients with unknown RAS status will be summarized as a separate group with all other patients if there are enough patients. Otherwise the efficacy data will be listed.

[redacted]

10.5.2 Safety objectives

10.5.2.1 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 and tumor types.

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 treatment
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study treatment
3. Post-treatment period: starting at day 31 after last dose of study treatment.

Safety summaries will primarily be based on all data from the on-treatment period. Following last administration of study treatment, adverse events (including serious adverse events), and new antineoplastic therapies are collected for a period of 150 days. Following start of new antineoplastic therapy only treatment related adverse events will be collected. Select summaries of related adverse events will be produced for the combined on-treatment and post-treatment periods (see Section 10.5.2.2).

10.5.2.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. Additional 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 adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by tumor type and treatment group.

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

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

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

All safety data from the patients from Japanese safety run-in part will be summarized separately. More details will be provided in the SAP.

10.5.2.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per CTCAE version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

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

[redacted]

For laboratory tests where grades are not defined by CTCAE 4.03, results will be categorized as low/normal/high) based on laboratory normal ranges.

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

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

For laboratory tests where grades are defined by CTCAE 4.03:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE 4.03 grades to compare baseline to the worst on-treatment value

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

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

10.5.2.4 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 SAP.

- Shift table baseline to worst on-treatment result

10.5.2.5 Supportive analyses for secondary objectives

Any supportive analyses that are considered appropriate for secondary variables will be described in the SAP prior to database lock (DBL).

10.5.2.6 Tolerability

Tolerability of study drug treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by patient and summarized.

[redacted]

10.5.3.1 Outline of the data analysis

As a project standard, the data collected from tumor samples in the clinical database will be analyzed by a Novartis designated laboratory and Novartis Oncology study team.

[redacted]

If the number of samples is inadequate to perform a rigorous data analysis, then only the available data will be listed. Additional analyses that may be performed after the completion of the end-of-study clinical study report will be documented in separate reports. Any additional data analysis will be described in an addendum of the RAP or in a stand-alone analysis plan document, as appropriate.

10.5.3.2 Data handling principles

All measurements below their respective Lower Limit of Quantification (LLOQ) or missing data will be labeled as such in the concentration data listings. Measurements below the LLOQ will be treated as zero in summary statistics. Change from baseline analyses will only be performed on patients with measurable samples and pre- and post-treatment time points.

10.5.3.3 Data analysis principles

10.5.3.3.1 Analysis sets

Patients with measureable tumor samples will be identified in the summaries and relevant proportion will be calculated against this number of patients.

[redacted]

10.5.3.3.3 Advanced analysis methods

Any methods that may be used will be described in the SAP.

10.5.4 Pharmacokinetics

All patients who have evaluable PK data will be included in the PK data analysis. PK parameters will be determined using non-compartmental method(s) for NIR178 and its metabolite and PDR001. PK parameters such as those listed in Table 10-2 will be estimated and reported, when applicable. [redacted]

[redacted]

Table 10-2 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/F	The total body clearance of drug from the plasma (volume x time-1)
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)

10.5.4.1 Data handling principles

Only PK blood samples with the date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. Missing concentration values will be reported as is in data listings. Concentration values below Lower limit of quantitation (LLOQ) will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

10.5.4.1.1 Basic tables, figures and listings

Descriptive statistics (mean, standard deviation, CV% or median (range)) will be presented for all parameters by analyte, tumor types and treatment groups and study cycle/day. When a geometric mean is presented, it will be stated as such. 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 presented for this parameter. For NJI765, CL/F, Vz/F and elimination half-life will not be reported.

PK data for Japanese safety run-in part will be reported separately.

[redacted]

[redacted]

10.5.5 Resource utilization

Not applicable.

[redacted]

10.5.6 Patient-reported outcomes

Not applicable.

[redacted]

10.7 Interim analysis

Part 1:

Patients will be continuously accrued and the data will be analyzed using a Bayesian hierarchical model mentioned in Section 10.4.2. Interim analysis for a tumor type will be performed when at least 10 patients which have been enrolled for that tumor type at the same dose level have at least one post-baseline disease assessment, except for MSS-CRC RAS wildtype, MSS-CRC RAS mutant and RCC IO naive at 240 mg patients, in which no interim analysis will be done. The futility analysis will not be binding. At each of these analyses, the current (posterior) probability that the response rate for each of the tumor types is greater than "clinically meaningful threshold (column for C2 in Table 10-1)" will be determined.

These probabilities will be used to adapt the design. All available data for evaluable patients (defined in Section 10.4.3) will be used for analysis at each interim analysis. However, a decision will be made for all tumor types with minimum of 10 patients (who have at least one post-baseline assessment). For a specific tumor type, a decision will be made based on the calculated probability as given below:

1. Accrual to a tumor type (with minimum sample size requirement described above) will cease for futility if it is very unlikely (posterior probability <20%) that the response rate for the tumor type is "clinically meaningful" (≥C2 threshold in Table 10-1)
2. Otherwise, recruitment will continue until the next IA is performed or a maximum of 30 patients in that tumor type has been enrolled.

For the purpose of the IA, if a patient is still on study and the last available efficacy assessment is a PR/CR which is yet to be confirmed by a subsequent scan, then this patient will be considered as a responder.

[redacted]

The results at the final analysis within a tumor type will be regarded as positive if the posterior mean ORR is greater than the threshold for clinically relevant activity and the posterior probability of not being clinically meaningful is low (less than 10%).

Depending on enrollment, there may be multiple interim analyses.

Japanese safety run-in part

No formal interim analyses are planned. However, the dose-escalation design for safety run-in part foresees that decisions based on the current data are taken before the end of the planned safety run-in part. Details of this procedure and the process for communication with Investigators are provided in Section 4.1.4.

10.8 Sample size calculation

Part 1:

The design of this part is adaptive in nature; hence, the final sample size is not fixed. A minimum of 10 evaluable patients and a maximum of 30 treated patients in each tumor type T1 through T13 will receive treatment. Thus, the total sample size across all tumor types will be between 130 and 310.

Patients will be continuously accrued, and, the accumulated data will be analyzed at interim as described in Section 10.7. Based upon the results of any of these analyses, enrollment into one or more tumor types may be terminated.

The operating characteristics for this Bayesian Design are evaluated using simulation. Simulation-based probability estimates (relative frequencies) of futility at interim and positive results at final analysis for each tumor type in four scenarios (see Table 14-12) are provided in Appendix 4. The number of simulations generated for each scenario is 1000. For additional details, please see Appendix 4. Presented below is a summary of the operating characteristics based on eight tumor types included in the initial protocol design prior to interim analysis:

Table 14-13 (Scenario 1) presents the operating characteristics of the design when the true underlying ORR of none the eight tumor types is clinically meaningful (in other words, null case for all tumor types). The false positive rate (for final analysis) for each of the tumor types are appropriately controlled, ranging between 2.6% and 6.8%. Similarly, the chances of stopping for futility at IA are high, ranging from 45.8% to 69.7%.

Table 14-14 presents the operating characteristics for two scenarios (2a and 2b):

- Scenario 2a presents the operating characteristics when the true underlying ORR of all the eight tumor types is clinically meaningful (in other words, alternative case for all tumor types). The probability of positive conclusion (for final analysis) for each of the tumor types are appropriately high, ranging between 78.2% and 90.7%. Similarly, the chances of stopping for futility at IA are low, ranging between 3% and 11.9%.
- Scenario 2b, in contrast to Scenario 2a, presents the case where, out of all eight tumor types there is one single tumor type (T4-Bladder) which does not have clinically meaningful ORR while all other seven tumor types have clinically meaningful ORR. However, the model adapts appropriately and the false positive rate (1.1%) for T4 is

[redacted]

effectively controlled. For the rest seven tumor types which have clinically meaningful ORR (same as Scenario 2a), the probability of positive conclusion has slightly changed (vs Scenario 2a) but remained acceptably high (ranging between 79.6% and 88.7%).

Table 14-15 (Scenario 3) presents the operating characteristics when four tumor types have clinically meaningful ORR while the other four do not have clinically meaningful ORR. In this scenario as well, the false positive rates for the inactive tumor types are properly controlled (4.9% - 6.9%) while the probability of positive conclusion for the active tumor types are high (78.2% - 86.6%).

Similar operating characteristics are expected based on the thirteen tumor groups.

Part 2:

At least 20 patients will be enrolled in each of the dosing schedules. Table 10-3 shows the posterior mean and corresponding 90% credible interval for N = 20 (since it is planned to have approximately 20 patients in each schedule) for various observed ORR using a minimally informative unimodal beta prior distribution with parameters a = 1/3 and b = 1 (note: this assumes a priori response rate of 25%). This is same for all dosing schedules.

Table 10-3 Posterior summaries for given number of responses (ORR)

Observed ORR (N, %)	Posterior mean (90% credible interval)	Probability of no improvement [0% - 20%)	Probability of limited improvement [20% - 33%)	Probability of clinically meaningful improvement [33%-100%]
0 (0%)	0.016 (0.00,0.070)	0.999	0.001	0.000
3 (15%)	0.156 (0.051, 0.299)	0.744	0.228	0.028
4 (20%)	0.203 (0.081, 0.356)	0.534	0.385	0.080
5 (25%)	0.250 (0.115, 0.414)	0.316	0.498	0.185
10 (50%)	0.484 (0.311, 0.657)	0.002	0.070	0.928
15 (75%)	0.718 (0.548, 0.863)	0	0	1
20 (100%)	0.954 (0.866,0.997)	0	0	1

From Table 10-3, with a sample size of 20 patients, if the observed ORR is 25%, the probability of true ORR to be at least 33% is 18.5%. If the observed ORR is 50%, the probability of true ORR to be at least 33% is 92.8%. Also, with a sample size of 20, if the observed ORR is 15%, the probability of true ORR to be less than 20% is 74.4%.

Table 10-4 shows the posterior probability that ORR for schedule 1 (S1) is greater than ORR for schedule 2 (S2) for various observed ORR using a minimally informative unimodal beta prior distribution with parameters a = 1/3 and b = 1. Similar approach can be used to compare schedule 2 to schedule 3 and schedule 1 to schedule 3.

[redacted]

Table 10-4 Posterior probability that schedule 1 (S1) has higher ORR than schedule 2 (S2)

Observed ORR in S1 (N, %)	Observed ORR in S2 (N, %)	Posterior mean of the difference (90% credible intervals)	Probability that ORR in S1 is greater than ORR in S2 given data
3 (15%)	0 (0%)	0.141 (0.027, 0.287)	0.981
4 (20%)	3 (15%)	0.046 (-0.142, 0.236)	0.660
5 (25%)	4 (20%)	0.047 (-0.160, 0.254)	0.646
5 (25%)	5 (25%)	0.000 (-0.213, 0.212)	0.499
10 (50%)	5 (25%)	0.234 (-0.001, 0.459)	0.949
10 (50%)	8 (40%)	0.095 (-0.152, 0.336)	0.740
15 (75%)	10 (50%)	0.235 (-0.003, 0.463)	0.948
15 (75%)	12 (60%)	0.140 (-0.094, 0.371)	0.839
20 (100%)	15 (75%)	0.235 (0.071, 0.414)	0.990

From Table 10-4, with a sample size of 20 patients in each schedule, the posterior probability that ORR in S1 is greater than ORR in S2 is 50% if the difference between observed ORR in the two schedules is 0% respectively. However, if the difference between observed ORR in S1 and S2 is 5% respectively, the posterior probability that ORR in S1 is greater than ORR in S2 is approximately 65.0%. If the difference between observed ORR in S1 and S2 is 25% respectively, the posterior probability that ORR in S1 is greater than ORR in S2 is approximately 95.0%.

Table 10-5 Posterior probability that schedule 1 (S1) has higher ORR than both schedule 2 (S2) and schedule 3 (S3)

Observed ORR in S1 (N, %)	Observed ORR in S2 (N, %)	Observed ORR in S3 (N, %)	Probability that ORR in S1 is greater than ORR in S2 and S3 given data
3 (15%)	0 (0%)	0 (0%)	0.963
4 (20%)	3 (15%)	3 (15%)	0.509
5 (25%)	4 (20%)	3 (15%)	0.568
5 (25%)	5 (25%)	5 (25%)	0.335
10 (50%)	5 (25%)	5 (25%)	0.911
10 (50%)	8 (40%)	5 (25%)	0.719
15 (75%)	10 (50%)	10 (50%)	0.906
15 (75%)	12 (60%)	10 (50%)	0.814
20 (100%)	15 (75%)	12 (60%)	0.990

From Table 10-5, with a sample size of 20 patients in each schedule, the posterior probability that ORR in S1 is greater than ORR in both S2 and S3 is 33.5% if the difference between observed ORR in the three schedules is 0% respectively. However, if the observed ORR in S1, S2 and S3 are 10%, 8% and 5% respectively, the posterior probability that ORR in S1 is greater than ORR in both S2 and S3 is 71.9%.

[redacted]

Part 3:

If initiated, 20 patients will be enrolled in each of the one or two tumor groups (max two) selected based on emerging data from Part 1 and Part 2. For the one or two tumor groups selected in Part 3, appropriate intervals will be defined and specified before any reporting activity in the statistical analysis plan. Novartis may decide to not open Part 3 for enrollment based on emerging data from Part 1 and Part 2.

As of protocol amendment 6, 20-30 patients will enroll in TNBC tumor group using NIR178 continuous dosing schedule in combination with PDR001. A second tumor group may be considered for Part 3 after completion of Part 1, see Section 4.1.3.

A sample size of 10 patients treated at 160 mg BID FCT NIR178 in combination with PDR001 in TNBC tumor group in Part 3 provides a high probability, 77%, of observing 0 or 1 adverse event when the true incidence rate is 9%. (Table 10-6).

Table 10-6 Probability of detecting adverse events with specified incidence rate based on N=10 patients

Number of adverse events	AE incidence rate			
	0.05	**0.09**	**0.12**	**0.15**
0 or 1	0.91	0.77	0.66	0.54
2 or 3	0.09	0.22	0.32	0.41
>3	0.00	0.01	0.02	0.05

Regarding the efficacy of part 3, Table 10-7 shows the posterior mean and corresponding 95% credible interval for N=20 for various observed ORR rates using a minimally informative unimodal beta prior distribution with parameters a=0.176 and b=1 for TNBC patients (Note: this assumes a priori response rate of 15%). From Table 10-7, with a sample size of 20 patients, if the observed ORR rate is 15%, the probability of true ORR rate for TNBC patients to be at least 13% is 54.8%

Table 10-7 Posterior mean and 95% credible intervals for given ORR rates

ORR (N, %)	Posterior mean (95% credible interval)	Probability of no improvement [0% - 5%]	Probability of limited improvement (5%-13%)	Probability of clinically meaningful improvement [13%-100%]
0(0%)	0.008 (0.00,0.066)	0.958	0.038	0.004
2 (10%)	0.103 (0.015, 0.259)	0.220	0.495	0.285
3 (15%)	0.150 (0.036, 0.326)	0.060	0.392	0.548
4 (20%)	0.197 (0.062, 0.386)	0.012	0.217	0.771
5 (25%)	0.244 (0.091, 0.443)	0.002	0.092	0.906
10 (50%)	0.481 (0.277, 0.688)	0.000	0.000	1.000

[redacted]

Japanese safety run-in part

The period for evaluating DLTs will be cycle 1 (i.e. the first 28 days of treatment with single agent NIR178 or in combination with PDR001). The safety run-in will evaluate three NIR178 dose levels sequentially. Each dose level may consist of 3 to 6 newly enrolled patients who have tumor histologies specified in Section 5, and meet all other inclusion/exclusion criteria. The dose escalation is detailed in Section 4.1.4.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

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

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.

[redacted]

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.

During the COVID-19 pandemic that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on 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 (icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

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

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

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

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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.

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.

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11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

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

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14 Appendices

14.1 Appendix 1: Concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or NIR178 and/or PDR001.

The following lists are not comprehensive and are only meant to be used as a guide. The lists are based on the Oncology Clinical Pharmacology guidance, Drug-Drug Interaction and Co-Medication Considerations (v07, release date: 2018), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (/medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (October 2017) (/fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (druginteractioninfo.org/). For current lists of medications that may cause QT prolongation, refer to the CredibleMeds® website (crediblemeds.org/). Please contact the Novartis medical monitor with any questions.

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Table 14-1 List of prohibited medications

Category	Drug Names
Strong inhibitors of CYP1A2	Ciprofloxacin (also known risk of TdP/QT prolongation), clinafloxacin, enoxacin, fluvoxamine, rofecoxib, Zafirlukast, Angelicae dahuricae radix extract (Angelica dahurica)
Moderate inducers of CYP1A2	montelukast, phenytoin, cigarette smoking, rifampin, eriflunomide, ritonavir, *Cannabis sativa* smoking
Substrates of CYP1A2 with narrow therapeutic index	theophylline, tizanidine (also sensitive substrate)
Sensitive substrates of CYP1A2	alosetron, duloxetine, melatonin, pirfenidone, ramelteon, selegiline, tacrine, tasimelteon, tizanidine
Drugs with known TdP risk/QT prolongation	Aclarubicin (not on US mkt), amiodarone, anagrelide, arsenic trioxide, astemizole (off US mkt), azithromycin, bepridil (off US mkt), chloroquine, chlorpromazine, cilostazol, cisapride (off US mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US mkt), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin (off mkt in North America), grepafloxacin (off market worldwide), halofantrine, haloperidol, ibogaine (not on US mkt), ibutilide, levofloxacin, , levomepromazine (methotrimeprazine [not on US mkt]), levomethadyl (off mkt worldwide), levosulpiride (not on US mkt), mesoridazine (off mkt worldwide), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol (off mkt worldwide), procainamide (oral off US mkt), propofol, quinidine, roxithromycin (not on US mkt), sevoflurane, sotalol, sparfloxacin (off US mkt), sulpiride (not on US mkt), sultopride (not on US mkt), terfenadine (off US mkt), terlipressin (not on US mkt), terodiline (not on US mkt), thioridazine, vandetanib

Table 14-2 List of medications to be used with caution

Category	Drug Names
Moderate inhibitors of CYP1A2	3,4-methylene-dioxymethamphetamine (MDMA), idrocilamide, methoxsalen (8-methoxypsoralen), mexiletine, oral contraceptives, phenylpropanolamine, pipemidic acid, propafenone, propranolol, troleandomycin, vemurafenib, genistein
Weak inhibitors of CYP1A2	Acyclovir,allopurinol, antofloxacin, artemisinin, caffeine (and caffeine containing products (also sensitive substrate of CYP1A2), cimetidinem curcuminm daidzein, deferasirox, disulfiram, echinacea (Echinacea purpurea), famotidine, grapefruit juice, grepafloxacin, hormone replacement therapy, interferon alpha, interferon beta, norfloxacin, pefloxacin, peginterferon alpha-2a, simeprevir, sirukumab, terbinafine, thiabendazole, ticlopidine, verapamil, viloxazine, zileuton Seijo-bofu-to, genistein
Substrates of BCRP	Atorvastatin, daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax

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14.2 Appendix 2: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free and Overall Survival (based on RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

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Version 3:0: 19-Oct-2009
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Authors (Version 1): [redacted]

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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
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical analysis plan
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

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14.2.1 Introduction

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

The efficacy assessments described in Section 14.2.2 and the definition of best response in Section 14.2.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.2.18 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 14.2.28 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

14.2.2 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.

14.2.3 Definitions

14.2.4 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 14.2.26.

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.

14.2.5 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 14.2.26.

14.2.6 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to 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 anti-tumor 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.

[redacted]

- 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 unknown (UNK) overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET:** can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound:** When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy:** The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when tumor samples are obtained.

[redacted]

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

14.2.7 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.2.4.
- **Nodal target:** See Section 14.2.4.

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.

[redacted]

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-3) and non-target lesions (Table 14-4) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-5) as well as the presence or absence of new lesions.

14.2.9 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.

14.2.10 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.

14.2.11 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.

[redacted]

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

14.2.12 Determination of target lesion response

Table 14-3 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 14.2.6.

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the eCRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-3 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.

[redacted]

- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements:** In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size:** When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split:** In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced:** Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
    - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
    - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
    - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

[redacted]

14.2.13 Determination of non-target lesion response

Table 14-4 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 treatment. treatment 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 14.2.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

[redacted]

14.2.14 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued treatment and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
  - If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.2.15).
- 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 14.2.6.

14.2.15 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 14-5.

Table 14-5 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 14.2.8.

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

[redacted]

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall response 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.

14.2.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.2.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.2.17 Best overall response

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

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

[redacted]

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.

[redacted]

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

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

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

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

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

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

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).

[redacted]

14.2.18 Time to event variables

14.2.19 Progression-free survival

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

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

14.2.20 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

14.2.21 Time to progression

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

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.2.22 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.

[redacted]

14.2.23 Duration of response

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

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

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

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

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

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

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

14.2.24 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.

[redacted]

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 14.2.23. 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.

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

Assessment date

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

Start dates

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

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

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

[redacted]

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 14.2.26).

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 treatment is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

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

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

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-6.

[redacted]

Table 14-6 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 14.2.8.

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.

14.2.27 Sensitivity analysis

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 SAP 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 14.2.25, 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 14-7 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 SAP	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 14.2.25.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.2.25.
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 14-7 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 SAP documentation.

14.2.28 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).

14.2.29 Study/project specific decisions

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

14.2.30 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.

[redacted]

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

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

14.2.31 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 Novartis

14.2.32 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

[redacted]

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 SAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

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

14.2.33 Programming rules

The following should be used for programming of efficacy results:

14.2.34 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.

14.2.35 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 14.2.25). 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.

14.2.36 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.

14.2.37 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)'.

[redacted]

14.2.38 Study/project specific programming

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

14.2.39 Censoring reason

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

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-7)
- Death due to reason other than underlying cancer
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.2.25. 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.

[redacted]

14.2.40 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.

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]

14.3 Appendix 3: iRECIST Guidelines for response in trials testing immunotherapeutics

14.3.1 Introduction

This appendix outlines the definitions and rules for response assessment in cancer immunotherapy trials (iRECIST) following the guideline developed by the RECIST working group using modified RECIST 1.1 (Seymour 2017, EORTC website).

Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size of malignant lesions, or undetectable lesions becoming detectable ('pseudoprogression'). The iRECIST criteria are identical to RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

14.3.1.1 Terminology

All responses defined using iRECIST criteria are designated with the prefix 'i' in order to differentiate them from responses assigned using RECIST 1.1. Additionally, an overall response of progression may be unconfirmed (iUPD) or subsequently confirmed (iCPD). New lesions are evaluated and subcategorized into those that qualify as target lesions (New Lesion Target; NLT), while all others are referred to as non-target (New Lesion Non-Target; NLNT).

14.3.1.2 iRECIST

RECIST 1.1 (Appendix 14.2) should be followed to define whether tumor lesions, including lymph nodes, are measurable or non-measurable; for the management of bone lesions, cystic lesions and lesions with prior local treatment (such as radiation); for the handling of lesions that become too small to measure, split or coalesce; and for recommendations regarding the method of measurement.

The principles used to determine objective tumor response are largely unchanged from RECIST 1.1, while a major change of iRECIST is the concept of 'resetting the bar' if RECIST 1.1 progression is followed at the next assessment by tumor shrinkage.

[redacted]

14.3.2 iRECIST response assessment

14.3.2.1 Confirming progression

iRECIST defines iUPD (i.e. unconfirmed progression) based on RECIST 1.1 principles. However, unlike RECIST 1.1, iRECIST requires the confirmation of progression (iCPD). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is evident by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an **increase** in tumor burden
  - **Increase** in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesion types (target or non-target or new lesions) where progression was **not** previously identified, including the appearance of additional new lesions.

14.3.2.2 Assessments following unconfirmed progression (iUPD)

If iUPD is not confirmed at the next assessment, but instead tumor shrinkage (compared to baseline) occurs then an overall response of iCR, iPR or iSD may be assigned as appropriate. Note that new lesions do not need to resolve for iSD or iPR to follow iUPD, provided an increase in size or number of new lesions does not lead to iCPD.

Following iCR, iPR, or iSD the bar is reset so that iUPD must occur again (compared to nadir values) and then be confirmed (by further growth) at the next assessment for iCPD (confirmed progression) to be assigned.

If there is no change in tumor size/extent from iUPD, then the response assessment would again be iUPD.

As can be seen in Table 14-8, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent assessments providing that iCPD is not documented at the next assessment after iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood and better characterized.

[redacted]

14.3.2.3 New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria, and recorded as New Lesions-Target (NLT) or New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions. A maximum of 5 NLT may be recorded, no more than 2 per organ, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions).

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of NLTs should not be included in the sum of measures (SOM) of original target lesions identified at baseline. These measurements will be collected on a separate case report form (CRF).

14.3.2.4 Confirming response

As for RECIST 1.1, responses (iCR or iPR) should also be confirmed under iRECIST by a repeat assessment not less than 4 weeks after the criteria for response are first met. Should an unconfirmed response be followed by an assessment of iUPD, then the response will remain as unconfirmed, and any subsequent return to response will again require confirmation. For example, a patient is assessed as iPR, and is subsequently assessed as iUPD then iPR again. This would not be considered as confirmed iPR unless the second occurrence of iPR is confirmed (e.g., sequence of assessments: iPR-iUPD-iPR-iPR; date of confirmed PR would be the date of the third of these assessments).

[redacted]

14.3.2.5 Examples of iResponse assignation

Table 14-8 Time Point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD*	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/ Non-iPD	No	iPR	iPR
iPR	Non-iCR/ Non-iUPD	No	iPR	iPR
iSD	Non-iCR/ Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD.
iSD, iPR, iCR	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in SOM of at least 5mm
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • Previously identified T lesion iUPD SOM ≥5mm and/or • NT lesion iUPD (prior assessment – need not be unequivocal progression)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • Previously identified T lesions iUPD ≥5mm and/or • Previously identified NT lesion iUPD (need not be unequivocal) and/or • Size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on • Increase in size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same.

** in any lesion category.

*** identified in the assessment immediately prior to this assessment.

14.3.3 References (available upon request)

Seymour L, Bogaerts J, Perrone A (2017) iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol; 18:e143-e152.

[redacted]

14.4 Appendix 4: Details of statistical methodology

This section provides the details of model stated in Section 10.4.2 for Part 1 of the study. Prior specifications of model parameters are provided in details. Data analysis and decision making in real trial are illustrated using some hypothetical data scenarios. Further operating characteristics by simulation are provided in Section 10.8 as part of sample size justification.

Section 14.4.1 to Section 14.4.3 are part of the original protocol with 8 tumor groups. Section 14.4.4 has been added to consider new groups (MSS CRC RAS wildtype, MSS CRC RAS mutant and HNSCC pretreated). Moreover, Section 14.4.5 has been added at the time of the amendment 5 when two more tumor groups have been included in the study (i.e. RCC IO pretreated at 240mg and mCRPC at 240mg). Prior specification of model parameters in Section 14.4.1 is applicable to Section 14.4.4. – Section 14.4.5.

14.4.1 Prior specification of model parameters

Bayesian model requires prior specification of parameters. The detailed prior specification of μ_1, μ_2, τ_1, τ_2, m_w, v_w, and p_j (j= 1,2,..,8) are described in this section.

14.4.1.1 Prior specification of exchangeability distribution (μ_1, μ_2, τ_1 and τ_2)

Prior for τ_1 and τ_2 are assumed to be half-normal distribution with scale 0.25, implying a prior 95% intervals for τ_1 and τ_2 as (0.008, 0.560), which allows for small to substantial between strata heterogeneity (see Spiegelhalter et al 2004).

μ_1 and μ_2 are given normal prior distributions. For first exchangeability distribution μ_1, the mean of the prior distribution ($m_{\mu 1}$) is set to logit(0.15) (or $m_{\mu 1}$ = log(3/17)) which corresponds to no treatment effect. For second exchangeability distribution μ_2, the prior mean ($m_{\mu 2}$) was set to logit(0.6) (or $m_{\mu 2}$ = log(3/2)). This corresponds to a substantial treatment effect. The variance parameter ($V_{\mu 1}$ and $V_{\mu 2}$) are derived using the following formula from law of total variance

$$V_{\mu i} = V(\theta) - E(\tau_i^2) \text{ and } V(\theta)=1/\pi + 1/(1- \pi); \pi= 0.15, 0.60 \text{ and } i=1,2$$

This yields $V_{\mu 1}$ = 7.781 ($\approx 2.789^2$) and $V_{\mu 2}$ = 4.104 ($\approx 2.026^2$). This allows a considerable uncertainty on prior belief of θ.

14.4.1.2 Prior specification for stratified or "non-exchangeability" distributions (m_w and v_w)

The strata-specific normal priors for the stratified or "non-exchangeable" case are defined by m_w and v_w were. The prior median for the response probability was set as 10% (no treatment effect) i.e., m_w = logit(0.1) (or m_w = log(1/9)) and the corresponding variance (v_w) is set to 9 ($=3^2$) to allow large variability in prior.

[redacted]

14.4.1.3 Specification of mixture weights (p_j)

Finally, for each stratum j, the prior mixture weights p_j were chosen as

$$p_j = (0.25, 0.25, 0.50), j=1,\ldots,8.$$

This means that each stratum has 25% prior probability to belong to the first exchangeability distribution (μ_1 and τ_1), 25% probability to belong to the second exchangeability distribution (μ_2 and τ_2), and 50% probability to be stratified or non-exchangeable with some (or all) of the other strata.

The prior distributions are summarized in Table 14-9, which also shows the prior medians and 95% credible intervals for the overall response rate (ORR) π_j.

Table 14-9 Specifications for model parameters, and prior median (95 percent credible intervals) for ORR

Parameter	Prior distribution
μ_1	$N(-1.735, 2.789^2)$
μ_2	$N(0.405, 2.026^2)$
τ_1	Half Normal(scale = 0.25)
τ_2	Half Normal(scale = 0.25)
m_j, v_j	$N(-2.197, 3^2)$
$p_j = (p_{j1}, p_{j2}, p_{j3})$, j = 1,…,8	(0.25, 0.25, 0.5)

14.4.2 Hypothetic scenario testing

It is important to know that the design should make reasonable decisions at interim and final analysis based on the observed responses in each tumor type. This section shows on-study decisions made under the model. The hypothetical data scenarios for interim and final analysis can be found in Table 14-10 and Table 14-11 respectively. For each scenario, the posterior probability of being "clinically meaningful" and "not clinically meaningful" (Table 10-1) are calculated by tumor type and displayed in the tables.

Table 14-10 shows 9 different scenarios for interim analyses. The scenarios show one or more tumor types having 10 patients. It is to be noted that the decision to stop or continue enrollment of patients in that tumor type is made only if the number of patients in that tumor type is at least 10. Otherwise, no decision is made. As stated in Section 10.7 at interim, a tumor type is stopped if the probability of being "clinically meaningful" is less than 20%.

At interim, if tumor type with at least 10 patients does not show any activity (scenarios 1, 2 and 3) the decision based on model are reasonable. The posterior probabilities of "clinically meaningful" are less than 20% for all tumor types in all scenarios for scenario 3 (Column 6 of Table 14-11) and hence further enrollment is stopped in all the tumor types. Similarly for scenarios 4, 5 and 6 where all tumor types show some clinically meaningful activity the proposed decision rule suggests to "continue" for the tumor types which had enrolled 10 patients (posterior probability of "clinically meaningful" > 20%). The proposed design also shows reasonable decision for mixed scenarios (7, 8 and 9). For example, under scenario 9, data for tumor types T2, T3, T5 and T8 show no clinically activity but the rest shows some activity. Based on the calculated probability of being clinically meaningful, the design allows correctly

[redacted]

stopping (probability < 0.20) for T2, T3, T5 and T8 at the interim while continues for the other tumor types.

Table 14-10 Hypothetical data scenarios and decision at interim

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Observed ORR	Posterior probability of clinically meaningful	Decision
1	T1	DLBCL	1/10	10%	0.1680	Stop
	T2	Pancreatic	0/6	0%	0.1232	-
	T3	H&N	2/7	28.57%	0.4122	-
	T4	Bladder	1/8	12.5%	0.0837	-
	T5	RCC	2/9	22.22%	0.0688	-
	T6	Colon (MSS)	1/9	11.11%	0.4495	-
	T7	TNBC	0/7	0%	0.1642	-
	T8	Melanoma	1/6	16.67%	0.0253	-
2	T1	DLBCL	1/10	10%	0.1385	Stop
	T2	Pancreatic	0/9	16%	0.0632	-
	T3	H&N	1/7	14.29%	0.1578	-
	T4	Bladder	0/8	0%	0.0108	-
	T5	RCC	2/10	20%	0.0482	Stop
	T6	Colon (MSS)	1/8	12.5%	0.4350	-
	T7	TNBC	0/7	0%	0.1432	-
	T8	Melanoma	2/10	20%	0.0198	Stop
3	T1	DLBCL	1/10	10%	0.1450	Stop
	T2	Pancreatic	0/10	0%	0.0390	Stop
	T3	H&N	0/10	0%	0.0098	Stop
	T4	Bladder	1/10	10%	0.0565	Stop
	T5	RCC	2/10	20%	0.0625	Stop
	T6	Colon (MSS)	0/10	0%	0.0688	Stop
	T7	TNBC	0/10	0%	0.0802	Stop
	T8	Melanoma	3/10	30%	0.1035	Stop
4	T1	DLBCL	3/8	37.5%	0.8792	-
	T2	Pancreatic	4/9	44.4%	0.9775	-
	T3	H&N	3/7	42.9%	0.8348	-
	T4	Bladder	3/10	30.0%	0.5805	Continue
	T5	RCC	2/9	22.2%	0.1362	-
	T6	Colon (MSS)	1/7	14.3%	0.7045	-
	T7	TNBC	1/8	12.5%	0.6548	-
	T8	Melanoma	2/8	25.0%	0.0855	-

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Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Observed ORR	Posterior probability of clinically meaningful	Decision
5	T1	DLBCL	3/8	37.5%	0.9085	-
	T2	Pancreatic	4/10	40.0%	0.9785	Continue
	T3	H&N	3/7	42.9%	0.8890	-
	T4	Bladder	3/8	37.5%	0.7600	-
	T5	RCC	2/9	22.2%	0.2098	-
	T6	Colon (MSS)	1/7	14.3%	0.6998	-
	T7	TNBC	2/10	20.0%	0.8430	Continue
	T8	Melanoma	5/10	50.0%	0.4378	Continue
6	T1	DLBCL	2/10	20.0%	0.5922	Continue
	T2	Pancreatic	2/10	20.0%	0.7355	Continue
	T3	H&N	2/10	20.0%	0.4658	Continue
	T4	Bladder	3/10	30.0%	0.5048	Continue
	T5	RCC	4/10	40.0%	0.3535	Continue
	T6	Colon (MSS)	2/10	20.0%	0.8215	Continue
	T7	TNBC	1/10	10.0%	0.5608	Continue
	T8	Melanoma	5/10	50.0%	0.3932	Continue
7	T1	DLBCL	2/8	25.0%	0.5460	-
	T2	Pancreatic	0/6	0.0%	0.1698	-
	T3	H&N	2/10	20.0%	0.3380	Continue
	T4	Bladder	2/9	22.2%	0.2545	-
	T5	RCC	1/7	14.3%	0.0435	-
	T6	Colon (MSS)	1/9	11.1%	0.5522	-
	T7	TNBC	1/7	14.3%	0.6260	-
	T8	Melanoma	3/9	33.3%	0.1172	-
8	T1	DLBCL	2/8	25.0%	0.6012	-
	T2	Pancreatic	0/6	0.0%	0.1495	-
	T3	H&N	1/10	10.0%	0.1713	Stop
	T4	Bladder	2/9	22.2%	0.3180	-
	T5	RCC	2/7	28.6%	0.2095	-
	T6	Colon (MSS)	0/10	0.0%	0.1095	Stop
	T7	TNBC	1/7	14.3%	0.5918	-
	T8	Melanoma	5/10	50.0%	0.4365	Continue
9	T1	DLBCL	2/10	20.0%	0.5138	Continue
	T2	Pancreatic	0/10	0.0%	0.0870	Stop
	T3	H&N	0/10	0.0%	0.0260	Stop
	T4	Bladder	3/10	30.0%	0.4185	Continue
	T5	RCC	2/10	20.0%	0.0503	Stop
	T6	Colon (MSS)	2/10	20.0%	0.7872	Continue
	T7	TNBC	2/10	20.0%	0.7900	Continue
	T8	Melanoma	3/10	30.0%	0.0762	Stop

Similar to interim, Table 14-11 shows 6 different hypothetical scenarios for final analyses in order to illustrate final decision making process in the proposed design. As stated in Section 10.4.2 at final a Proof of Concept (PoC) about treatment with NIR178 in combination with PDR001 will be declared for a tumor type if both of the following conditions are met:

a. posterior mean ORR (Column 5) ≥ "Clinically meaningful" threshold (C_2) (Column 6)
b. Posterior probability of "not being clinically meaningful" (Column 7) is less than 10%

If no tumor type shows any significant activity (scenario 1 and 2) at final analysis, the decision using the model are reasonable (declared fail to support PoC for all tumor types that made to the final analysis). The posterior probabilities of "not clinically meaningful" are greater than 10% for all tumor types in scenario 2 (Column 7 of Table 14-11). Similarly for scenario 4 where all tumor types show clinically meaningful activity the proposed decision rule (to be declared success) leads to PoC for all tumor types (posterior probability of "not clinically meaningful" < 10% and posterior means of ORR are more than "clinically meaningful" threshold (Column 6 of Table 14-11)). The proposed design also shows reasonable decision for mixed scenarios (5 and 6). For example, under scenario 6, data for tumor types T2, T3, T6 and T8 show no clinically activity but the rest of the tumor types show activity. Based on the posterior probability of being not clinically meaningful and posterior mean of ORR, the design correctly declared failure for T2, T3, T6 and T8 while success for the other tumor types.

Table 14-11 Hypothetical data scenarios and decision at final

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Posterior mean ORR	Clinically meaningful threshold (C_2)	Posterior probability of not clinically meaningful	Decision
1	T1	DLBCL	3/30	0.0950	0.20	0.6142	Fail
	T2	Pancreatic	0/10	0.0448	0.16	0.8222	-
	T3	H&N	0/10	0.0441	0.23	0.9388	-
	T4	Bladder	2/30	0.0735	0.27	0.9435	Fail
	T5	RCC	2/10	0.1643	0.37	0.8080	-
	T6	Colon (MSS)	1/30	0.0495	0.13	0.5840	Fail
	T7	TNBC	1/30	0.0494	0.13	0.5795	Fail
	T8	Melanoma	3/10	0.2508	0.43	0.6715	-
2	T1	DLBCL	4/30	0.1373	0.20	0.2915	Fail
	T2	Pancreatic	2/30	0.0850	0.16	0.5240	Fail
	T3	H&N	3/30	0.1104	0.23	0.6875	Fail
	T4	Bladder	4/30	0.1367	0.27	0.6242	Fail
	T5	RCC	7/30	0.2117	0.37	0.7290	Fail
	T6	Colon (MSS)	1/30	0.0551	0.13	0.5310	Fail
	T7	TNBC	1/30	0.0559	0.13	0.5168	Fail
	T8	Melanoma	9/30	0.2656	0.43	0.6820	Fail

[redacted]

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Posterior mean ORR	Clinically meaningful threshold (C_2)	Posterior probability of not clinically meaningful	Decision
3	T1	DLBCL	7/30	0.2259	0.20	0.0140	Success
	T2	Pancreatic	0/10	0.0520	0.16	0.7535	-
	T3	H&N	0/10	0.0509	0.23	0.8668	-
	T4	Bladder	10/30	0.2968	0.27	0.0135	Success
	T5	RCC	2/10	0.2045	0.37	0.7200	-
	T6	Colon (MSS)	4/30	0.1557	0.13	0.0282	Success
	T7	TNBC	4/30	0.1558	0.13	0.0228	Success
	T8	Melanoma	3/10	0.2561	0.43	0.7068	-
4	T1	DLBCL	7/30	0.2351	0.20	0.0107	Success
	T2	Pancreatic	5/30	0.1886	0.16	0.0290	Success
	T3	H&N	7/30	0.2355	0.23	0.0427	Success
	T4	Bladder	9/30	0.2890	0.27	0.0220	Success
	T5	RCC	13/30	0.3967	0.37	0.0485	Success
	T6	Colon (MSS)	4/30	0.1634	0.13	0.0208	Success
	T7	TNBC	4/30	0.1644	0.13	0.0242	Success
	T8	Melanoma	15/30	0.4610	0.43	0.0345	Success
5	T1	DLBCL	7/30	0.2146	0.20	0.0190	Success
	T2	Pancreatic	0/10	0.0538	0.16	0.7375	-
	T3	H&N	0/10	0.0529	0.23	0.8625	-
	T4	Bladder	6/30	0.1931	0.27	0.2585	Fail
	T5	RCC	2/10	0.1855	0.37	0.8055	-
	T6	Colon (MSS)	4/30	0.1482	0.13	0.0268	Success
	T7	TNBC	2/30	0.0916	0.13	0.2552	Fail
	T8	Melanoma	3/10	0.2430	0.43	0.7560	-
6	T1	DLBCL	7/30	0.2424	0.20	0.0160	Success
	T2	Pancreatic	2/30	0.0835	0.16	0.5407	Fail
	T3	H&N	3/30	0.1139	0.23	0.6625	Fail
	T4	Bladder	9/30	0.2918	0.27	0.0230	Success
	T5	RCC	13/30	0.3901	0.37	0.0365	Success
	T6	Colon (MSS)	1/30	0.0525	0.13	0.5695	Fail
	T7	TNBC	4/30	0.1457	0.13	0.0298	Success
	T8	Melanoma	9/30	0.2893	0.43	0.5660	Fail

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14.4.3 Operating characteristics

14.4.3.1 Scenarios

In order to demonstrate the operating characteristics of the design, four scenarios have been considered. The scenarios have been presented in Table 14-12.

1. Scenario 1 presents the case where the true underlying ORR of none the eight tumor types is clinically meaningful (in other words, null case for all tumor types).
2. Scenario 2a presents the case where the true underlying ORR of all the eight tumor types is clinically meaningful (in other words, alterative case for all tumor types).
3. Scenario 2b presents the case where only one single tumor type (T4-bladder) does not have clinically meaningful ORR but all other seven tumor types have clinically meaningful ORR (same as Scenario 2a).
4. Scenario 3 presents the case where four tumor types have clinically meaningful ORR while the other four do not have clinically meaningful ORR.

Table 14-12 True underlying ORR (percent) in the four scenarios

Disease Code	Tumor Type	True ORR (%)			
		Sce 1 (All tumor types inactive)	Sce 2a (All tumor types active)	Sce 2b (One single tumor type inactive, other seven active)	Sce 3 (Four tumor types active, four other inactive)
T1	DLBCL	10.0	**30.0**	**30.0**	10.0
T2	Pancreatic	8.0	**25.0**	**25.0**	**25.0**
T3	H&N	13.0	**35.0**	**35.0**	13.0
T4	Bladder	15.0	**35.0**	10.0	15.0
T5	RCC	25.0	**50.0**	**50.0**	**50.0**
T6	Colon (MSS)	5.0	**20.0**	**20.0**	5.0
T7	TNBC	5.0	**20.0**	**20.0**	**20.0**
T8	Melanoma	30.0	**58.0**	**58.0**	**58.0**
Clinically significant responses are shown in bold font.					

14.4.3.2 Simulation details

In all four scenarios (Table 14-12), it is assumed that an average accrual rate per tumor type is 2 patients per group every month on average. The number of simulations generated for each scenario is 1000.

14.4.3.2.1 Metrics to assess operating characteristics

In a given tumor type, the type I error (false positive rate) of the adaptive design can be viewed as the probability estimate of a positive conclusion at final analysis in Scenario 1 (Table 14-13). The power of the adaptive design is defined as the probability estimate of positive conclusion at final analysis in Scenario 2a (Table 14-14).

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14.4.3.2.2 Results

Table 14-13 (Scenario 1) presents the operating characteristics of the design when the true underlying ORR of none the eight tumor types is clinically meaningful (in other words, null case for all tumor types). The false positive rate (for final analysis) for each of the tumor types are appropriately controlled, ranging between 2.6% and 6.8%. Similarly, the chances of stopping for futility at IA are high, ranging from 45.8% to 69.7%.

Table 14-13 Simulation results for Scenario 1 (NIR178 and PDR001 combination inactive for all tumor types)

Disease code	Tumor type	True ORR (%)	Probability of stopping at IA for futility (%)	Probability for positive conclusion in final analysis (%)
T1	DLBCL	10.0	64.3	4.2
T2	Pancreatic	8.0	45.8	6.8
T3	H&N	13.0	61.9	5.1
T4	Bladder	15.0	65.7	2.6
T5	RCC	25.0	69.7	4.1
T6	Colon (MSS)	5.0	59.8	5.8
T7	TNBC	5.0	59.8	5.8
T8	Melanoma	30.0	65.0	3.8

Table 14-14 presents the operating characteristics for two scenarios (2a and 2b):

- Scenario 2a presents the operating characteristics when the true underlying ORR of all the eight tumor types is clinically meaningful (in other words, alternative case for all tumor types). The probability of positive conclusion (for final analysis) for each of the tumor types are appropriately high, ranging between 78.2% and 90.7%. Similarly, the chances of stopping for futility at IA are low, ranging between 3% and 11.9%.
- Scenario 2b, in contrast to Scenario 2a, presents the case where, out of all eight tumor types there is one single tumor type (T4-Bladder) which does not have clinically meaningful ORR while all other seven tumor types have clinically meaningful ORR. However, the model adapts appropriately and the false positive rate (1.1%) for T4 is effectively controlled. For the rest seven tumor types which have clinically meaningful ORR (same as Scenario 2a), the probability of positive conclusion has slightly changed (vs Scenario 2a) but remained acceptably high (ranging between 79.6% and 88.7%).

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Table 14-14 Simulation results for Scenario 2a (all tumor types active) and Scenario 2b (one single tumor type [T4-Bladder] inactive, all other active)

Disease code	Tumor type	True ORR (%)		Probability of stopping at IA for futility (%)		Probability for positive conclusion in final analysis (%)	
		2a	2b	2a	2b	2a	2b
T1	DLBCL	30.0	30.0	3.0	4.0	90.7	88.7
T2	Pancreatic	25.0	25.0	6.6	6.6	86.7	86.2
T3	H&N	35.0	35.0	4.5	6.7	90.5	87.6
T4	Bladder	35.0	10.0	9.7	72.8	78.2	1.1
T5	RCC	50.0	50.0	6.9	8.6	82.5	80.5
T6	Colon (MSS)	20.0	20.0	11.9	11.9	79.5	79.6
T7	TNBC	20.0	20.0	11.9	11.9	79.5	79.6
T8	Melanoma	58.0	58.0	7.6	8.4	83.9	84.1
Tumor type which has different ORR between the two scenarios has been shaded. Clinically significant responses are shown in bold font.							

Table 14-15 (Scenario 3) presents the operating characteristics when four tumor types have clinically meaningful ORR while the other four do not have clinically meaningful ORR. In this mixed scenario as well, the false positive rates for the inactive tumor types are appropriately controlled (4.9% - 6.9%) while the probability of positive conclusion for the active tumor types are high (78.2% - 86.6%).

Table 14-15 Simulation results for scenario 3 (four tumor types active while other four inactive)

Disease code	Tumor type	True ORR (%)	Probability of stopping at IA for futility (%)	Probability for positive conclusion in final analysis (%)
T1	DLBCL	10.0	48.9	5.9
T2	Pancreatic	25.0	6.8	84.3
T3	H&N	13.0	58.2	5.7
T4	Bladder	15.0	55.8	4.9
T5	RCC	50.0	10.6	82.2
T6	Colon (MSS)	5.0	59.8	6.9
T7	TNBC	20.0	11.9	78.2
T8	Melanoma	58.0	8.4	86.6
The tumor types which are assumed to be clinically meaningful are shown in bold fonts.				

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14.4.4 Hypothetical scenario testing after addition of new groups

This section was added after the inclusion of MSS CRC RAS mutant, MSS CRC RAS wildtype and HNSCC pretreated groups. For the updated version with 13 tumor groups, please see Section 14.4.5.

This section shows on-study decisions made under the model after the new groups are added. The hypothetical data scenarios for interim and final analysis can be found in Table 14-16 and Table 14-17 respectively. For each scenario, the posterior probability of being "clinically meaningful" and "not clinically meaningful" (T1-T10 in Table 10-1) are calculated by group and displayed in the tables.

Table 14-16 shows 6 different scenarios for interim analyses. The scenarios show one or more groups having 10 or more patients. It is to be noted that the decision to stop or continue enrollment of patients in that group is made only if the number of patients in that group is at least 10. Otherwise, no decision is made. As stated in Section 10.7 at interim, a group is stopped if the probability of being "clinically meaningful" is less than 20%.

Scenario 1 and 2 shows two possible scenarios with the current data. There are 17 MSS CRC patients with 1 responder. The data for mutation status of CRC patients are not available but will be collected retrospectively after implementation of this protocol amendment. Hence, two different scenarios are considered. In scenario 1, we considered 2 out of the 17 patients are RAS mutant patients and 15 out of 17 patients have RAS status unknown. Hence the patients with unknown RAS status are not included in the model. One of the two RAS mutant patients is a responder. In scenario 2, we considered 2 out of 17 patients are RAS mutant patients and 7 out of 17 patients are RAS wildtype patients. The other 8 patients have RAS status unknown. One of the two RAS mutant patients is a responder. We will have 20 additional patients in the MSS CRC RAS wildtype and mutant group after expansion.

Based on the interim analysis done, the decision was made to expand to 30 patients in TNBC (T6). Decision was also made to enroll 20 additional patients to CRC RAS-wildtype (T9) and CRC RAS-mutant (T10) groups. Also, it was decided to stop further enrollment in Pancreatic (T2) group. Hence no decision will be made in the subsequent interim analyses for these groups, although the data will be included in the statistical model. Hence Scenario 3-6 does not show any decisions for T2, T6, T9 and T10. Further decisions to stop enrollment or to expand will be made for groups DLBCL (T1), HNSCC naive (T3), Urothelial (T4), RCC (T5), Melanoma pre (T7) and HNSCC pre (T8).

At interim, if a group with at least 10 patients does not show any activity (scenarios 3 and 4) the decision based on model are reasonable. The posterior probabilities of "clinically meaningful" are less than 20% for all groups that are ongoing and have not expanded for scenario 3 (Column 6 of Table 14-16) and hence further enrollment is stopped in all these groups. Similarly for scenario 6 where all groups show some clinically meaningful activity the proposed decision rule suggests to "continue" for the groups which had enrolled 10 patients (posterior probability of "clinically meaningful" > 20%). The proposed design also shows reasonable decision for mixed scenario 5. For example, under scenario 5, data for groups T4 and T5 show no clinically activity but T1, T3, T7 and T8 shows some activity. Based on the calculated probability of being clinically meaningful, the design allows correctly stopping (probability < 0.20) for T4 and T5 at the interim while continues for the other groups.

[redacted]

Table 14-16 Hypothetical data scenarios and decision at interim

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Observed ORR	Posterior probability of clinically meaningful response	Decision
1	T1	DLBCL	1/6	16.7%	0.3340	-
	T2	Pancreatic	0/14	0%	0.0295	Stopped
	T3	HNSCC naive	1/7	14.3%	0.2175	-
	T4	Urothelial	1/8	12.5%	0.1090	-
	T5	RCC	1/5	20.0%	0.1038	-
	T6	TNBC	2/13	15.4%	0.5748	Expanded
	T7	Melanoma pre	0/0	-	0.3312	-
	T8	HNSCC pre	0/0	-	0.5425	-
	T9	CRC-RAS wt	0/0	-	0.5328	Expanded
	T10	CRC-RAS mu	½	50%	0.8062	Expanded
2	T1	DLBCL	1/6	16.7%	0.3027	-
	T2	Pancreatic	0/14	0%	0.0282	Stopped
	T3	HNSCC naive	1/7	14.3%	0.1910	-
	T4	Urothelial	1/8	12.5%	0.0942	-
	T5	RCC	1/5	20.0%	0.0810	-
	T6	TNBC	2/13	15.4%	0.5618	Expanded
	T7	Melanoma pre	0/0	-	0.3080	-
	T8	HNSCC pre	0/0	-	0.5208	-
	T9	CRC-RAS wt	0/7	0%	0.1538	Expanded
	T10	CRC-RAS mu	½	50%	0.7810	Expanded
3	T1	DLBCL	1/10	10.0%	0.1108	Stop
	T2	Pancreatic	0/14	0%	0.0212	-
	T3	HNSCC naive	1/11	9.1%	0.0558	Stop
	T4	Urothelial	1/10	10.0%	0.0365	Stop
	T5	RCC	1/10	10.0%	0.0082	Stop
	T6	TNBC	4/18	22.2%	0.7395	-
	T7	Melanoma pre	0/10	0%	0.0060	Stop
	T8	HNSCC pre	1/5	20%	0.5190	-
	T9	CRC-RAS wt	0/12	0%	0.0660	-
	T10	CRC-RAS mu	1/8	12.5%	0.3938	-
4	T1	DLBCL	1/10	10.0%	0.0832	Stop
	T2	Pancreatic	0/14	0%	0.0102	-
	T3	HNSCC naive	1/11	9.1%	0.0405	Stop
	T4	Urothelial	1/10	10.0%	0.0275	Stop
	T5	RCC	1/10	10.0%	0.0050	Stop
	T6	TNBC	2/13	15.4%	0.3912	-
	T7	Melanoma pre	0/10	0%	0.0032	Stop
	T8	HNSCC pre	0/10	0%	0.0565	Stop
	T9	CRC-RAS wt	0/17	0%	0.0207	-
	T10	CRC-RAS mu	1/12	8.3%	0.2023	-

[redacted]

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Observed ORR	Posterior probability of clinically meaningful response	Decision
5	T1	DLBCL	2/10	20.0%	0.4670	Continue
	T2	Pancreatic	0/14	0%	0.0557	-
	T3	HNSCC naive	2/11	18.2%	0.2932	Continue
	T4	Urothelial	2/10	20.0%	0.1758	Stop
	T5	RCC	2/10	20.0%	0.0328	Stop
	T6	TNBC	5/18	27.8%	0.9512	-
	T7	Melanoma pre	2/10	20.0%	0.2368	Continue
	T8	HNSCC pre	2/10	20.0%	0.8128	Continue
	T9	CRC-RAS wt	3/17	17.6%	0.8065	-
	T10	CRC-RAS mu	2/12	16.6%	0.7695	-
6	T1	DLBCL	2/10	20.0%	0.5578	Continue
	T2	Pancreatic	0/14	0%	0.0520	-
	T3	HNSCC naive	2/11	18.2%	0.3780	Continue
	T4	Urothelial	3/10	30.0%	0.4025	Continue
	T5	RCC	4/10	40.0%	0.2522	Continue
	T6	TNBC	5/18	27.8%	0.9658	-
	T7	Melanoma pre	2/10	20.0%	0.3332	Continue
	T8	HNSCC pre	2/10	20.0%	0.8385	Continue
	T9	CRC-RAS wt	3/17	17.6%	0.8405	-
	T10	CRC-RAS mu	2/12	16.6%	0.8042	-

Similar to interim, Table 14-17 shows 6 different hypothetical scenarios for final analyses in order to illustrate final decision making process in the proposed design. As stated in Section 10.4.2 at final a Proof of Concept (PoC) about treatment with NIR178 in combination with PDR001 will be declared for a tumor type if both of the following conditions are met:

posterior mean ORR (Column 5) ≥ "Clinically meaningful" threshold (C_2) (Column 6)

Posterior probability of "not being clinically meaningful" (Column 7) is less than 10%

If no group shows any significant activity (scenario 1 and 2) at final analysis, the decision using the model are reasonable (declared fail to support PoC for all groups that made to the final analysis). The posterior probabilities of "not clinically meaningful" are greater than 10% for all groups in scenario 2 (Column 7 of Table 14-17). Similarly for scenario 4 where all groups show clinically meaningful activity the proposed decision rule (to be declared success) leads to PoC for all groups (posterior probability of "not clinically meaningful" < 10% and posterior means of ORR are more than "clinically meaningful" threshold (Column 6 of Table 14-17). The proposed design also shows reasonable decision for mixed scenarios (5 and 6). For example, under scenario 6, data for groups T3, T4, T7 and T10 show no clinically activity but the rest of the groups show activity. Based on the posterior probability of being not clinically meaningful and posterior mean of ORR, the design correctly declared failure for T3, T4, T7 and T10 while success for the other groups.

[redacted]

Table 14-17 Hypothetical data scenarios and decision at final

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Posterior mean ORR	Clinically meaningful threshold (C_2)	Posterior probability of not clinically meaningful response	Decision
1	T1	DLBCL	3/30	0.0990	0.20	0.5685	Fail
	T2	Pancreatic	0/14	0.0416	0.16	0.8178	-
	T3	HNSCC naive	1/11	0.0949	0.23	0.7960	-
	T4	Urothelial	2/30	0.0807	0.27	0.9500	Fail
	T5	RCC	2/10	0.1467	0.37	0.8742	-
	T6	TNBC	2/30	0.0806	0.13	0.2170	Fail
	T7	Melanoma pre	1/30	0.0589	0.25	0.4300	Fail
	T8	HNSCC pre	1/10	0.0999	0.13	0.5952	-
	T9	CRC-RAS wt	3/27	0.1026	0.13	0.0825	Fail
	T10	CRC-RAS mu	3/22	0.1155	0.13	0.0545	Fail
2	T1	DLBCL	4/30	0.1251	0.20	0.3125	Fail
	T2	Pancreatic	0/14	0.0444	0.16	0.7632	-
	T3	HNSCC naive	3/30	0.1097	0.23	0.7212	Fail
	T4	Urothelial	4/30	0.1240	0.27	0.7640	Fail
	T5	RCC	6/30	0.1618	0.37	0.9085	Fail
	T6	TNBC	3/30	0.1088	0.13	0.0620	Fail
	T7	Melanoma pre	2/30	0.0911	0.25	0.1720	Fail
	T8	HNSCC pre	2/30	0.0902	0.13	0.6188	Fail
	T9	CRC-RAS wt	3/27	0.1149	0.13	0.0482	Fail
	T10	CRC-RAS mu	3/22	0.1246	0.13	0.0350	Fail
3	T1	DLBCL	7/30	0.2234	0.20	0.0098	Success
	T2	Pancreatic	0/14	0.0381	0.16	0.8302	-
	T3	HNSCC naive	1/11	0.1428	0.23	0.4568	-
	T4	Urothelial	10/30	0.2852	0.27	0.0142	Success
	T5	RCC	2/10	0.2019	0.37	0.7358	-
	T6	TNBC	4/30	0.1585	0.13	0.0202	Success
	T7	Melanoma pre	9/30	0.2643	0.25	0.0000	Success
	T8	HNSCC pre	1/10	0.1482	0.13	0.3095	-
	T9	CRC-RAS wt	4/27	0.1708	0.13	0.0125	Success
	T10	CRC-RAS mu	4/22	0.1933	0.13	0.0048	Success

[redacted]

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Posterior mean ORR	Clinically meaningful threshold (C_2)	Posterior probability of not clinically meaningful response	Decision
4	T1	DLBCL	7/30	0.2377	0.20	0.0068	Success
	T2	Pancreatic	0/14	0.0364	0.16	0.8452	-
	T3	HNSCC naive	9/30	0.2781	0.23	0.0052	Success
	T4	Urothelial	9/30	0.2760	0.27	0.0165	Success
	T5	RCC	13/30	0.3761	0.37	0.0628	Success
	T6	TNBC	4/30	0.1699	0.13	0.0155	Success
	T7	Melanoma pre	9/30	0.2776	0.25	0.0000	Success
	T8	HNSCC pre	5/30	0.1946	0.13	0.0598	Success
	T9	CRC-RAS wt	4/27	0.1822	0.13	0.0115	Success
	T10	CRC-RAS mu	4/22	0.2086	0.13	0.0045	Success
5	T1	DLBCL	7/30	0.2082	0.20	0.0162	Success
	T2	Pancreatic	0/14	0.0420	0.16	0.7930	-
	T3	HNSCC naive	1/11	0.1331	0.23	0.5055	-
	T4	Urothelial	10/30	0.2854	0.27	0.0247	Success
	T5	RCC	2/10	0.1826	0.37	0.8240	-
	T6	TNBC	4/30	0.1481	0.13	0.0145	Success
	T7	Melanoma pre	4/30	0.1478	0.25	0.0190	Fail
	T8	HNSCC pre	1/10	0.1337	0.13	0.3400	-
	T9	CRC-RAS wt	4/27	0.1581	0.13	0.0132	Success
	T10	CRC-RAS mu	3/22	0.1511	0.13	0.0230	Success
6	T1	DLBCL	7/30	0.2121	0.20	0.0160	Success
	T2	Pancreatic	0/14	0.0390	0.16	0.8170	-
	T3	HNSCC naive	3/30	0.1300	0.23	0.5157	Fail
	T4	Urothelial	9/30	0.2616	0.27	0.0470	Fail
	T5	RCC	13/30	0.3956	0.37	0.0620	Success
	T6	TNBC	5/30	0.1733	0.13	0.0048	Success
	T7	Melanoma pre	5/30	0.1733	0.25	0.0030	Fail
	T8	HNSCC pre	5/30	0.1740	0.13	0.0800	Success
	T9	CRC-RAS wt	4/27	0.1632	0.13	0.0130	Success
	T10	CRC-RAS mu	2/22	0.1267	0.13	0.1100	Fail

[redacted]

14.4.5 Addition of RCC naive, RCC pretreated group and mCRPC group at NIR178 240 mg BID

This section shows on-study decisions made under the statistical model with the three additional tumor groups included in the protocol amendment 5 (i.e RCC IO naive, RCC IO pretreated patients and mCRPC all treated at 240 mg BID dose of NIR178 in combination with PDR001. The hypothetical data scenarios for interim and final analysis can be found in Table 14-18 and Table 14-19 respectively.

Table 14-18 shows 4 different scenarios for the interim analyses, where one or more groups having 10 or more patients treated. It has to be noted that the decision to stop or continue enrollment of patients in that group is made only if the number of patients in a group is at least 10. As stated in Section 10.7 a group is stopped at interim if the probability of being "clinically meaningful" is less than 20%.

Scenario 1 considers the current available data, which is subject to change.

Based on the last interim analysis done, the decision was made to enroll 20 more patients to CRC RAS-wildtype (T9) at 160 mg NIR178 and CRC RAS-mutant (T10) at 160 mg NIR178. Decision was also made to stop enrolling RCC naive patients at 160 mg BID NIR178 (T5) and expand RCC naive patients at 240 mg BID NIR178 (T12) as a separate group. Final decision has also been made for TNBC (T6) group. Also, it was decided to stop further enrollment in Pancreatic (T2) and Urothelial (T4) groups. Hence, no further decisions will be made in the subsequent interim analyses for these groups, although the data will be included in the statistical model. Further decisions to stop enrollment or to expand will be made for groups DLBCL (T1), HNSCC naive (T3), Melanoma pre (T7), HNSCC pre (T8), RCC IO pretreated (T11), and mCRPC (T13).

For Scenario 2, none of the groups with at least 10 patients shows any activity (at interim, the relative posterior possibilities of "clinically meaningful" are less than 20%). In Scenario 3, for all groups that show some clinically meaningful activity with at least 10 patients treated, the proposed decision rule suggests to "continue" (posterior probability of "clinically meaningful" > 20%). The proposed statistical model shows reasonable decisions also under mixed scenarios 3 and 4.

Table 14-18 Hypothetical data scenarios and decision at interim

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Observed ORR	Posterior probability of clinically meaningful response	Decision
1	T1	DLBCL	1/10	10%	0.1060	Stop
	T2	Pancreatic	0/14	0%	0.0175	Decided to stop
	T3	HNSCC naive	2/9	22.2%	0.2788	-
	T4	Urothelial	1/14	7.1%	0.0135	Decided to stop
	T5	RCC naive at 160 mg	4/11	36.4%	0.3167	Decided to expand*
	T6	TNBC	3/30	10%	0.2468	Final
	T7	Melanoma pre	0/2	0%	0.0850	-
	T8	HNSCC pre	0/3	0%	0.1970	-

[redacted]

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Observed ORR	Posterior probability of clinically meaningful response	Decision
	T9	CRC-RAS wt	0/11	0%	0.0578	Decided to expand
	T10	CRC-RAS mu	1/19	5.3%	0.1148	Decided to expand
	T11	RCC pre at 240 mg	0/0	0%		-
	T12	RCC naive at 240	0/0	0%	0.3002	-**
	T13	mg mCRPC	0/0	0%	0.1805 0.1952	-
2	T1	DLBCL	1/10	10%	0.0782	Stop
	T2	Pancreatic	0/14	0%	0.0173	Decided to stop
	T3	HNSCC naive	2/11	18.2%	0.1427	Stop
	T4	Urothelial	1/14	7.1%	0.0082	Decided to stop
	T5	RCC naive at 160 mg	4/11	36.4%	0.2888	Decided to expand*
	T6	TNBC	3/30	10%	0.219	Final
	T7	Melanoma pre	0/10	0%	0.004	Stop
	T8	HNSCC pre	1/14	7.1%	0.176	Stop
	T9	CRC-RAS wt	0/11	0%	0.0538	Decided to expand
	T10	CRC-RAS mu	1/19	5.3%		Decided to expand
	T11	RCC pre at 240 mg	1/10	8.3%	0.1158	Stop
	T12	RCC naive at 240	0/0	0%	0.0795	-**
	T13	mg mCRPC	1/10	10%	0.161 0.0102	Stop
3	T1	DLBCL	3/10	30%	0.7235	Continue
	T2	Pancreatic	0/14	0%	0.0475	Decided to stop
	T3	HNSCC naive	3/11	27.3%	0.546	Continue
	T4	Urothelial	1/14	7.1%	0.051	Decided to stop
	T5	RCC naive at 160 mg	4/11	36.4%	0.2023	Decided to expand*
	T6	TNBC	3/30	10%	0.5088	Final
	T7	Melanoma pre	2/10	20%	0.324	Continue
	T8	HNSCC pre	2/10	20%	0.8358	Continue
	T9	CRC-RAS wt	3/14	0%	0.8815	Decided to expand
	T10	CRC-RAS mu	5/21	5.3%		Decided to expand
	T11	RCC pre at 240 mg	2/10	16.7%	0.946	Continue
	T12	RCC naive at 240	0/0	0%	0.5588	-**
	T13	mg mCRPC	4/10	40%	0.1905 0.3058	Continue
4	T1	DLBCL	3/10	30%	0.6038	Continue
	T2	Pancreatic	0/14	0%	0.025	Decided to stop
	T3	HNSCC naive	2/11	18.2%	0.2312	Continue
	T4	Urothelial	1/14	7.1%	0.0205	Decided to stop
	T5	RCC naive at 160 mg	4/11	36.4%	0.259	Decided to expand*
	T6	TNBC	3/30	10%	0.319	Final
	T7	Melanoma pre	0/10	0%	0.0118	Stop
	T8	HNSCC pre	1/10	10%	0.3852	Continue

[redacted]

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Observed ORR	Posterior probability of clinically meaningful response	Decision
	T9	CRC-RAS wt	0/11	0%	0.0905	Decided to expand
	T10	CRC-RAS mu	1/19	5.3%		Decided to expand
	T11	RCC pre at 240 mg	2/10	16.7%	0.1737	Continue
	T12	RCC naive at 240 mg	3/8	37.5%	0.3645	-**
	T13	mCRPC	1/10	10%	0.2725	Stop
					0.0168	

* Stopped enrolling RCC naive patients at 160 mg BID NIR178, decided to expand RCC naive patients at 240 mg BID NIR178 as a separate group.

** Enroll 20 more RCC naive patients at 240 mg BID NIR178 and no decision will be made at interim.

Similar to interim, Table 14-19 shows 4 different hypothetical scenarios for final analyses in order to illustrate final decision making process in the proposed design. For scenario 1, the posterior probabilities of "not clinically meaningful" are greater than 10% for all groups and hence none of the groups leads to success at final analysis. In scenario 2, for all groups that show clinically meaningful activity, the proposed decision rule leads to PoC for all groups (posterior probability of "not clinically meaningful" < 10% and posterior means of ORR are more than "clinically meaningful" threshold). The proposed statistical model shows reasonable decisions also under mixed scenarios 3 and 4.

Table 14-19 Hypothetical data scenarios and decision at final

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Posterior mean ORR	Clinically meaningful threshold (C_2)	Posterior probability of not clinically meaningful response	Decision
1	T1	DLBCL	1/10	0.0949	0.20	0.648	-
	T2	Pancreatic	0/14	0.0416	0.16	0.842	-
	T3	HNSCC naive	2/30	0.075	0.23	0.9288	Fail
	T4	Urothelial	1/14	0.0803	0.27	0.9155	-
	T5	RCC naive at 160 mg	4/11	0.304	0.37	0.399	-
	T6	TNBC	3/30	0.0913	0.13	0.1315	Final Decision made
	T7	Melanoma pre	1/14	0.0807	0.25	0.7338	-
	T8	HNSCC pre	1/10	0.0933	0.13	0.2332	-
	T9	CRC-RAS wt	0/11	0.0449	0.13	0.6142	-
	T10	CRC-RAS mu	1/19	0.07	0.13	0.3392	-
	T11	RCC pre at 240 mg	1/30	0.0547	0.20	0.9	Fail
	T12	RCC naive at 240 mg	3/20	0.1181	0.37	0.9512	Fail
	T13	mCRPC	2/30	0.0742	0.35	0.7915	Fail

[redacted]

Scenario	Tumor Code	Tumor Type	No of responder/ No of patients	Posterior mean ORR	Clinically meaningful threshold (C_2)	Posterior probability of not clinically meaningful response	Decision
2	T1	DLBCL	1/10	0.1276	0.20	0.456	-
	T2	Pancreatic	0/14	0.0377	0.16	0.8325	-
	T3	HNSCC naive	8/30	0.2598	0.23	0.0357	Success
	T4	Urothelial	1/14	0.103	0.27	0.788	-
	T5	RCC naive at 160 mg	4/11	0.3183	0.37	0.3182	-
	T6	TNBC	3/30	0.1153	0.13	0.0798	Final Decision made
	T7	Melanoma pre	3/24	0.1349	0.25	0.3325	-
	T8	HNSCC pre	3/27	0.1245	0.13	0.0712	-
	T9	CRC-RAS wt	0/11	0.0474	0.13	0.6492	-
	T10	CRC-RAS mu	1/19	0.0819	0.13	0.3342	-
	T11	RCC pre at 240 mg	7/30	0.2281	0.20	0.0265	Success
	T12	RCC naive at 240 mg	11/20	0.5005	0.37	0.0065	Success
	T13	mCRPC	12/30	0.3699	0.35	0	Success
3	T1	DLBCL	1/10	0.1225	0.20	0.4362	-
	T2	Pancreatic	0/14	0.041	0.16	0.8125	-
	T3	HNSCC naive	8/30	0.236	0.23	0.0588	Success
	T4	Urothelial	1/14	0.1033	0.27	0.793	-
	T5	RCC naive at 160 mg	4/11	0.2906	0.37	0.4525	-
	T6	TNBC	3/30	0.1134	0.13	0.0802	Final Decision made
	T7	Melanoma pre	4/30	0.1352	0.25	0.2795	Fail
	T8	HNSCC pre	1/10	0.1222	0.13	0.156	-
	T9	CRC-RAS wt	0/11	0.0489	0.13	0.6278	-
	T10	CRC-RAS mu	1/19	0.0845	0.13	0.3042	-
	T11	RCC pre at 240 mg	3/30	0.1133	0.20	0.4302	Fail
	T12	RCC naive at 240 mg	11/20	0.5154	0.37	0.0098	Success
	T13	mCRPC	6/30	0.1847	0.35	0.0662	Fail
4	T1	DLBCL	7/30	0.2111	0.20	0.0105	Success
	T2	Pancreatic	0/14	0.0397	0.16	0.8128	-
	T3	HNSCC naive	8/30	0.2328	0.23	0.031	Success
	T4	Urothelial	1/14	0.1217	0.27	0.6445	-
	T5	RCC naive at 160 mg	4/11	0.2771	0.37	0.503	-
	T6	TNBC	3/30	0.1342	0.13	0.058	Final Decision made
	T7	Melanoma pre	4/30	0.1572	0.25	0.1458	Fail
	T8	HNSCC pre	6/30	0.1944	0.13	0	Success
	T9	CRC-RAS wt	4/27	0.1653	0.13	0.0118	Success
	T10	CRC-RAS mu	6/28	0.2022	0.13	0.0008	Fail
	T11	RCC pre at 240 mg	3/30	0.1334	0.20	0.2798	Fail
	T12	RCC naive at 240 mg	11/20	0.5112	0.37	0.0168	Success
	T13	mCRPC	6/30	0.1936	0.35	0.0245	Fail

[redacted]

14.5 Appendix 5: Efficacy guideline for prostate cancer (based on PCWG3)

The predominant manifestations of progression of prostate cancers are rising prostate-specific antigen (PSA) values, new lesions on bone scan, new symptoms of disease, and an increase in a measurable tumor mass. Biochemical failure as represented by rising PSA is generally the first indication of recurring disease. Moreover, the prostate Cancer Clinical Trials Working Group emphasizes the importance of keeping patients on trial until radiographic or symptomatic progression, which better reflects a change in clinical status, is documented and that an effort is made not to discontinue therapy solely on the basis of a rise in PSA in the absence of other indicators of disease progression. This is particularly relevant for patients with low PSA values at entry and those with a slow rate of rise in PSA at progression (Scher et al 2016). Please refer to Table 14-19 for assessments and progression criteria on the basis of changes in PSA, bone metastases, and measurable disease (Scher et al 2016).

Table 14-20 PCWG3 criteria of progression by disease manifestation

Assessment	Evaluation Criteria for disease progression
PSA	Obtain sequence of rising values at a minimum of 1-week intervals 1 ng/mL minimum starting value if confirmed rise is only indication of progression unless pure small-cell carcinoma Estimate pre-therapy PSA-DT if 3 or more values available 4 or more weeks apart
Target lesions	Nodal or visceral progression sufficient for trial entry independent of PSA Measurable lesions not required for entry Use RECIST (v1.1) to record soft-tissue (nodal and visceral) lesions as target or non-target Previously normal (< 1.0-cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. If the node progresses to ≥ 1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy, progression is defined per RECIST 1.1 Record presence of nodal and/or visceral disease separately
Prostate	Record prior treatment of primary tumor Perform directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence or absence of disease
Bone	Progression = appearance of 2 or more new lesions Confirm ambiguous results by other imaging modalities (eg, CT or MRI), but only positivity on the bone scan defines metastatic disease to bone

Abbreviations: PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; PSA-DT, PSA doubling time; RECIST, Response Evaluation Criteria in Solid Tumors; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

Outcomes based on measurable disease and bone lesions

For the purposes of this study, patients should be reevaluated for response every 8 weeks using the RECIST Guideline v1.1 for radiological assessments and bone scans (if necessary).

[redacted]

Outcomes based on post-therapy PSA changes:

- **PSA Response (PR)**: Decrease in PSA value by >50% from baseline, confirmed by two successive evaluations at least three weeks apart.
- **Secondary PSA Response**: At least 30% decrease in PSA at ≥ 12 weeks from baseline which is confirmed at least 4 weeks later.
- **Stabilization (SD)**: Patients who do not meet the criteria for PR or POD will be considered stable
- **Progression (POD)**: A 25% or greater increase and an absolute increase of 2ng/mL or more from baseline (or after 12 weeks: ≥ 25% increase from nadir level) is documented, which is confirmed by a second value obtained 3 or more weeks later.
- **Time to PSA Progression**: The date that a 25% or greater increase and an absolute increase of 2ng/mL or more from baseline (or after 12 weeks: ≥ 25% increase from nadir) is documented, which is confirmed by a second value obtained 3 or more weeks later.

Progressive disease

Progressive disease will be based on POD and skeletal progression in addition to RECIST 1.1 (Appendix 1) and iRECIST (Appendix 2).

Reference section

Scher HI, Morris MJ, Stadler WM, et al (20016) Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol; 34:1402-18.

[redacted]

14.6 Appendix 6: Calculation - Cockcroft-Gault formula for GFR estimate

Creatinine clearance will be calculated using the following formulas:

- Male GFR = (140 - age) x (weight) / (sCr x 72)
- Female GFR = (140 - age) x (weight) x 0.85 / (sCr x 72)

GFR is Glomerular Filtration Rate in ml/min; Age is in years; Weight is Lean Body Mass in kilograms; sCr is Serum Creatinine in mg/dl

The formulas above should be altered in the following cases:

1. Overweight (GFR >25 kg/m2)
    a. Calculate based on adjusted body weight
    b. Adjusted body weight = wtKgIdeal + 0.4 * (wtKgActual - wtKgIdeal)
2. Underweight
    a. Use actual weight
    b. Do not round up to Serum Creatinine (significantly underestimates GFR)
3. Elderly
    a. Do not round up to Serum Creatinine (significantly underestimates GFR)
4. Amputation
    a. Measure 24 hour Creatinine Clearance

Wallach, J. Interpretation of Diagnostic Tests. Ed. 8 (2007) Lippincott Williams and Wilkins.

[redacted]