NOVARTIS

Clinical Development

NIR178, PDR001

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

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Final Amendment 2 (v2)
Release date:	12-Apr-2023
Number of pages:	64

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
12-Jan-2023	Prior to DB lock	Creation of final version per Protocol Amendment 6	The new TCO SAP template v4.0 is being used. Update per Protocol Amendment 6.	NA
12-Apr-2023	Prior to final DB Lock	Major/Minor changes	Final Amendment 2 (v2) <u>Major changes</u> - Updated list of abbreviations - Tightened the study design with regards to Protocol Amendments, introduced terminology for treatment indications, clarified contradictory statements andremoved duplicacy of information. - Distinguished efficacy and safety treatment groups for reporting on Part 1. Treatment indication precisely defined. - Precisely defined date of first/last administration of a study drug and study treatment - Corrected formula for Study day - Introduced different types of follow-ups as part of post-treatment period - Revised definition of Full analysis set - Revised definitions of IG analysis sets - Corrected the duration of exposure for Part 2 intermittant dosing - Aligned the organization of treatment indications with those mentioned Section 1.1.1 and Table 2-4 - Added a sentence to allow addition of any new qualifying treatment indication to inform the model. - Clarified that Secondary efficacy endpoints are to be evaluated inall Treatment groups contributing toprimary efficacy objective. - Time to event endpoints to be estimated for trt groups >= 10 patients - Added precise definition of “sufficient” number of patients for change from baseline PSA analysis. - Clarified the criteria for summarizing efficacy endpoints for unknown RAS status. - Moved the paragraph on Safety summary from Section 2.1.1.5 to the right section under Section 2.6.2 - Tightened the reporting of AEs, SAEs, Deaths in line with the protocol with listings required on Screen failure patients. - Clarified that AESIs associated with combination trt will be reported using PDR001-specific eCRS .	• List of abbreviations • Section 1.1 and sub-sections. • Section 2.1 • Section 2.1.1.2 • Section 2.1.1.3 • Section 2.1.1.5 • Section 2.2.1 • Section 2.2.4 • Section 2.4.1.1 • Section 2.5.2 • Table 2-4 • Section 2.5.2 • Section 2.6.1 • Section 2.6.1 • Section 2.6.1 • Section 2.6.1 • Section 2.6.2 • Section 2.6.2.1 • Section 2.6.2.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			- Corrected deliverables for EudraCT - Corrected the IG analysis to be in line with the latest IG protocol. - Corrected that changes in tumor immune infiltrate will be assessed by “change from baseline” and not “percentage” change. - Added a short description and reference to sample size estimation for addition of groups to Part 1after the first IA during the course of Phase II study. <u>Minor changes</u> - other minor editorial changes include grammatical corrections, sentence conciseness, replacement of “tumor types” redefined by “treatment indications” for preciseness where applicable.	• Section 2.6.2.4 • Section 2.6.5 • Section 2.6.7 • Section 3.1 • Throughout the document

Table of contents

List of abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under the Curve
BID	Bis In Die
CRF	Case Report Form
CSR	Clinical Study Report
CRO	Clinical Research Organization
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DI	Dose Intensity
DLBCL	Diffuse Large B Cell Lymphoma
DLT	Dose Limiting Toxicity
DMS	Document Management System
DoR	Duration of Response
ECG	Electrocardiogram
FAS	Full Analysis Set
FCT	Film Coated Tablet
HGC	Hard Gelatin Capsule
HNSCC	Head and Neck Cancer
IA	Interim Analyses
IB	Investigator's Brochure
IC	Non-tumor immune cell staining score
IHC	Immunohistochemistry
ITT	Intent to Treat
IV	Intra-Venious
mCRPC	metastatic castration resistant prostate cancer
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MSS CRC	Microsatellite Stable Colorectal Cancer
MTD	Maximum Tolerated Dose
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PCWG3	Prostate Cancer Working Group 3
PD	Phar
PDS	Programming Datasets Specifications
PFS	Progression Free Survival
PK	Pharmacokinetics
PD	Pharmacodynamic

PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PSA	Prostate-specific antigen
PT	Preferred Term
QD	Once Daily
RAP	Reporting & Analysis Process
RCC	Renal Cell Carcinoma
RD	Recommended Dose
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RR	RR interval (the distance between 2 consecutive R peaks)
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SAE	Serious Adverse Events
SD	Standard Deviation
SOC	System Organ Class
TFLs	Tables, Figures, Listings
TNBC	Triple-negative breast cancer
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes all planned analyses for the Clinical Study Report(s) (CSR) of study NIR178X2201, a phase II, multi-center, open label study of NIR178 in combination with PDR001 in patients with select advanced solid tumors and non-Hodgkin lymphoma (NHL).

The content of this SAP is based on NIR178X2201- Protocol Amendment 6. All decisions regarding interim analysis, as defined in the SAP document, have been made prior to database lock of the study data.

The output shells accompanying this document can be found in the Tables, Figures and Listings (TFL) shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document.

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

The SAP, TFL shells, and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., MTD/RD declaration, Investigator's Brochure (IB) updates, abstracts, posters, presentations, manuscripts, and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

1.1 Study design

This is an open-label multi-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 combination treatment, NIR178 + fixed PDR001 400 mg Q4W, until disease progression (assessed by investigator as per iRECIST (Appendix 3) for solid tumors, Cheson et al (2014) for DLBCL or PCWG3 guidelines for mCRPC), unacceptable toxicity, start of a new anti-neoplastic therapy, or discontinuation at investigator's or patient's discretion, lost to follow-up, death or study termination 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. [redacted]

Note: For the rest of the document, PDR001 400 mg Q4W will be referred to as 'PDR001'; patients receiving single agent (SA) NIR178 as 'SA patients' and those receiving combination treatment as 'combination patients'.

This phase II study has 3 parts (Figure 1-1). Parts 1 and 2 will enroll patients in parallel, and consequent to results from the two parts, Part 3 will open in not more than two select study

indications once recommended dose and dosing schedule is determined. The study parts have the following objectives:

- **Part 1**: Multi-arm Bayesian adaptive signal finding design in groups of 13 treatment indications - 9 tumor types including DLBCL, with categories based on mutation status or prior IO treatment, and assigned continuous dosing of NIR178 (160 mg BID or following Protocol Amendment 5, 240 mg BID) in combination with PDR001.

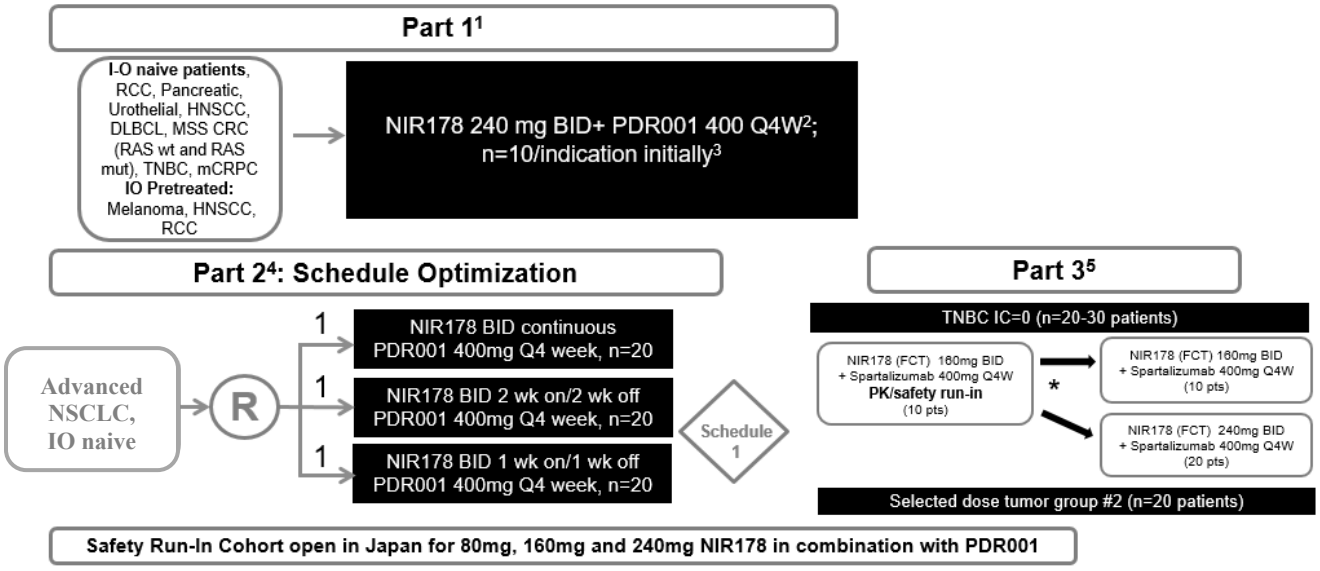
  Protocol Amendment 5 mandated administration of NIR178 240 mg BID + PDR001in all newly enrolled patients having any of the Part 1 indications or 2 newly added indications, mCRPC and RCC IO-pretreated, leading to 13 groups (see Section 2.5.2).
- **Part 2**: Exploration of continuous and intermittent schedules of NIR178 160 mg BID in combination patients with advanced non-small cell lung cancer (NSCLC).

  By the time Protocol Amendment 6 was formalized , this part was closed to enrollment and 'continuous' schedule was inferred as 'optimal'.
- **Part 3**: Further evaluation of 'optimal' NIR178 schedule (consequent to Part 2 results) in combination patients with selected Part 1 treatment indication.

  Protocol Amendment 6 opened enrollment to Part 3 for exploring the safety and pharmacokinetics of the new FCT formulation of NIR178 160 mg BID at 'continuous' schedule in combination TNBC patients with PD-L1 SP-142 IC score of 0 (<1%). Provision to add another Part 1 treatment indication to Part 3, contingent on Part 1 analysis, was introduced as well.

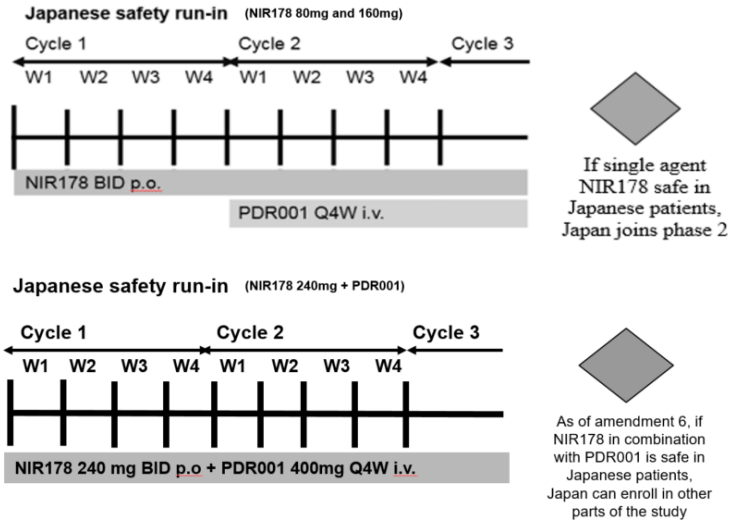
In addition to the Phase II study, a safety run-in study will be conducted in Japanese patients with treatment indications specified in the Phase II study parts to evaluate the safety and pharmacokinetic profiles of NIR178 as a single-agent or in combination with PDR001 (Figure1-2).
As of Protocol Amendment 6, total 6 patients were treated - 3 with SA NIR178 80mg and 3 with SA NIR178 160mg, during Cycle 1 and with PDR001 initiated at the beginning of Cycle 2 . This amendment required administration of NIR178 240 mg BID in combination with PDR001among all newly enrolled Japanese patients. The dose escalation algorithm is detailed in Section 1.1.4.

Figure 1-11 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 1-22 Study design- Japanese run-in part (NIR178 Single Agent and NIR178 +PDR001)



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

Part 1 of the study will enroll patients in the combination arm with the following treatment indications and NIR178 BID doses (160 mg at the study beginning and 240 mg consequent to Protocol Amendment 5): renal cell carcinoma (RCC) - IO naive (160 mg, 240 mg) and IO pretreated (240 mg), pancreatic cancer (160 mg), urothelial cancer (160 mg), squamous cell carcinoma of head and neck cancer (HNSCC) - IO naïve (160 mg) and IO pretreated (160 mg, 240 mg), microsatellite stable colorectal cancer (MSS CRC) - RAS wildtype (160 mg) and RAS mutant (160 mg), triple negative breast cancer (TNBC) (160 mg), cutaneous melanoma (BRAF V600E) (160 mg), diffuse large B-cell lymphoma (DLBCL) (160 mg, 240 mg), and metastatic castration resistant prostate cancer (mCRPC) (240 mg). Each indication will initially enroll at least 10 patients (with minimum requirements described in Protocol Section 4.2). Depending on whether or not pre-specified criteria for futility are met, each indication group may enroll up to a maximum of 30 patients with the exception of the MSS CRC RAS mutant and RAS wildtype groups, wherein 20 additional patients will be enrolled per group.

Accrual to each indication group in Part 1 will be based on futility assessment of observed ORR via non-binding interim analysis (IA) (explained below). The hierarchical model (see Section 2.5) is implemented to assess clinical significance of observed ORR, allowing dynamic borrowing of information between indications such that more borrowing occurs across those that have similar ORR and less borrowing occurs between those that 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 indication.

Note: For analysis, each of the indications - HNSCC IO pretreated & DLBCL, that has both 160 and 240 mg dose groups, was pooled into a single indication group due to limited observed responses, thus, maintaining the number of treatment indications contributing to the model to 13 that the study (Protocol Amendment 6) was designed for.

1.1.1.1 Timing of interim analyses and design adaptations

Given the adaptive enrollment model and signal finding nature of Part 1, multiple interim analyses (IAs) will be performed to either stop early for futility or enroll patients until the next IA is performed or indication-specific maximum enrollment is reached.

The first IA will occur when at least one indication group has accrued 10 patients who have at least one post-baseline disease assessment. Futility assessment at the first IA and subsequent IAs will inform a “go/no-go" decision for continuing enrollment in each indication group based on dynamic borrowing of ORR data across groups (See Protocol Section 10). Note: As of Protocol Amendment 6, the groups, RCC IO naïve (NIR178 240 mg BID) and MSS-CRC, were extension of the earlier cohorts - the former had new patients enrolled at 240 mg as a result of Protocol Amendment 5; and, the latter was split in two groups, RAS wild type and RAS mutant, with 20 patients each upon decision to expand enrollment at their respective IA.

Subsequent IAs will occur when one or more additional indication groups accrue 10 patients at the same dose level (with minimum requirements described before). While all available data will be used from all indications, the decision to stop early at the IA will be made only for indications with the minimum sample size requirement described above.

Non-binding: Novartis will have the flexibility to choose IA time points if it appears that multiple indications may qualify for IA requirements within a reasonable time between them. The futility assessment for an indication will not be binding even when the ORR-based early stopping criteria is met at respective IA. Novartis along with investigators may decide to continue enrolling patients to that indication group if comprehensive review of all available data suggests that the patients are receiving clinical benefit (Refer to Section 2.8).

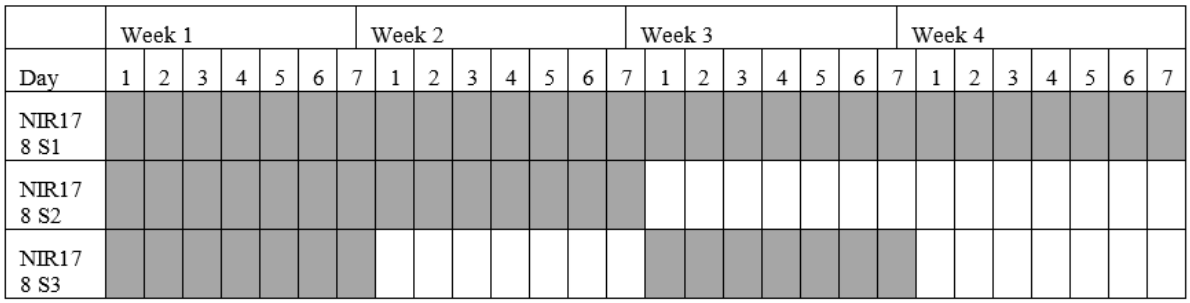
For an IA, if a patient is still on study and the last available efficacy assessment is a PR/CR which is yet to be confirmed by a subsequent scan, then this patient is considered a responder.

1.1.2 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. Each treatment group characterized by a different dosing schedule of NIR178 160 mg BID will enroll 20 patients. Eligible patients will be randomized in a 1:1:1 fashion to one of the 3 dosing schedules of NIR178 160mg BID (listed below) in combination with PDR001 within a 28-day cycle (Figure 1-3):

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

Figure 1-33 Alternate NIR178 dosing schedules within one cycle



The safety, tumor response rates, and tumor immune modulation of the intermittent NIR178 schedules (NIR178 S2 and S3) will be clinically assessed in comparison to that in the continuous schedule (NIR178 S1). Based on cumulative data (including safety, tolerability, [redacted] PK, [redacted]) across the three schedules, a dosing schedule may be selected by Novartis for further evaluation in Part 3 after documented discussion with study investigators.

Additionally, correlation between PD-L1 expression and response to PD-1 inhibitors in NSCLC will be further explored in a supportive analysis.

1.1.3 Part 3: NIR178+PDR001 additional exploration in selected treatment indications

Part 3 of the study will be an expansion of the optimal NIR178 dosing schedule (if selected) with the objective of further evaluating safety, efficacy, and immune modulation of the combination treatment with NIR178 dosing at "optimal"schedule in one or two select indication groups (from Part 1) of 20-30 patients. A maximum of 50 patients will be enrolled to this part, if initiated. The selected indications in Part 3 will be based on emerging data from Part 1 and Part 2. If one of the treatment indications selected for Part 3 is NSCLC, this group will enroll patients previously exposed to immunotherapy.

As of Protocol Amendment 6, the one selected indication group, TNBC, will have enrollment of patients with a known PD-L1 SP142 status of IC=0 (<1%) using a new FCT formulation of NIR178 at continuous dosing schedule in combination with PDR001. An additional indication group of 20 patients may be considered consequent to Part 1 analysis.

This part will initiate as PK/safety run-in of NIR178 160mg BID in combination with PDR001. After the first 10 patients complete at least 1 cycle of the study treatment, a safety analysis will be conducted to decide whether to escalate the NIR178 dose level to 240mg BID in newly enrolled patients or to complete Part 3 at NIR178 160mg BID. The dose escalation criteria is as follows:

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

Cumulative data (including safety, tolerability, [redacted] PK, [redacted]) will be reviewed on an ongoing basis by Novartis and study investigators via teleconferences.

1.1.4 Japanese safety run-in study

A separate safety run-in study will be conducted in Japan in order to adequately characterize the safety and pharmacokinetic profiles of NIR178 as a single-agent or in combination with PDR001(Figure 1-2). 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.

Based on the findings of CPDR001X1101 study, wherein no significant differences in the safety and PK of single agent PDR001 were found 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, the dose for PDR001 in the safety run-in of this sub-study will be 400 mg IV Q4 weeks.

Patients enrolled in the safety run-in part must be hospitalized for safety monitoring during the DLT evaluation period, which is the first cycle of therapy. Patients must complete a minimum of 80% of planned therapy during cycle 1 with the minimum required 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.

The safety run-in will initiate with evaluating two SA NIR178 dose levels sequentially:

1. NIR178 80mg BID continuous (1st dose level)
2. NIR178 160mg BID continuous

Following Protocol Amendment 6, the dose level: NIR178 240 mg BID continuous will be initiated in combination with PDR001 with 3 newly enrolled patients.

Each dose level may consist of 3 to 6 newly enrolled patients who have tumor histologies (see Protocol Section 5), and meet all other inclusion/exclusion criteria.

The first three patients enrolled to receive SA 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 1/3 SA patient at 80 mg experiences a DLT at the 80mg dose level, the safety run-in part will be terminated and Japanese patients will not join the phase II study.
- If 0/3 SA patients at 80 mg experience a DLT in cycle 1, evaluation of the 80 mg dose level will be complete and the next dose levelof SA, NIR178 160mg BID, will be initiated with 3 new patients unless Protocol Amendment 6 has been executed.
- If 0/3 SA patients at 160 mg 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. This is based on the findings from other studies wherein no obvious ethnic differences in safety and PK of single agent PDR001 were observed between Japanese versus non-Japanese patients and no DDI between NIR178 and PDR001 was observed.
- If 1/3 SA patients at 160 mg experience a DLT in cycle 1, 3 additional patients will be enrolled to this dose level. If ≤1/6 SA patients at 160mg experience DLT during cycle 1, 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 >1/3 SA patients at 160 mg experience a DLT in 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.

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

- If 0/3 combination patients at NIR178 240mg experience a DLT in cycle 1, NIR178 240mg BID + 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 1/3 combination patients at NIR178 240mg experience a DLT in cycle 1, 3 additional patients will be enrolled to this dose level. If ≤1/6 combination patients at NIR178 240mg experience DLT in cycle 1, NIR178 240mg BID + 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 >1/3 combination patients at NIR178 240mg experience a DLT in cycle 1, the safety-run-in part will be terminated and Japanese patients will not join the rest of the study.

Note: No interim analysis is planned for this study. The decision for dose escalation and to allow participation in phase II study will be based on all available safety data and the recommendation of participating investigators in Japan (Refer to Section 2.8).

1.2 Study objectives, endpoints and estimands

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

Table 1-11 Objectives and related endpoints

Objective	Endpoint
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

Objective	Endpoint
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
Secondary	
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
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)
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]

2 Statistical Methods

2.1 Data analysis general information

Study data will be analyzed by Novartis personnel and/or designated CRO(s) using the most updated SAS® version in the GPS environment. For the Bayesian analyses using R and/or WinBUGS and/or JAGS the most updated version in the MODESIM environment will be used. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 5.2 or later.

The study data will be reported at completion of the study, as defined in Protocol Section 4.3. A cutoff date will be established based on last patient last visit date. Statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g., vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

General analysis conventions

Pooling of centers: Unless otherwise specified, data from all study centers will be pooled for the analysis, so that an adequate number of patients will be available for analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

The data will be summarized and listed with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic (PK) [redacted] measurements. All tables, figures and listings (TFLs) will be presented by treatment groups specific to the study parts and safety/efficacy objective.

A **treatment group** will refer to patients receiving the same treatment (same type and dosage at the same schedule) for the same indication (tumor types with subgroups, based on mutation status or prior IO treatment), collectively termed as "*treatment indication*". Treatment will be presented at the most granular level determined by its type, dosage and schedule.

Phase II study

Note: As of Protocol Amendment 6, Part 1 constitutes patients receiving varying dose levels of combination treatment at the same schedule for varying indications; Part 2 constitutes patients receiving a single dose level of combination treatment at varying schedules for a single indication; and, Part 3 constitutes patients receiving same dose level at the same schedule for a single indication.

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

- Part 1: In general, all TFLs will be presented by *treatment indications* unless specified otherwise.

- Disposition, demographics and baseline characteristics: Treatment groups at the most granular levels of treatment indication will be used for reporting on disposition, analysis sets, demographics, disease history, prior treatment and other baseline characteristics. If in the given programming environment, presentation of summaries on all the treatment groups is visually constraining, then these summaries may be presented separately for safety and efficacy using their respective consolidated treatment groupings as defined below.
- Safety/PK/IG: Treatment groups at the dose level of any treatment indication consolidating the categories of indication (consolidated by tumor types with no sub-grouping) will be used for reporting on safety and related endpoints like PK/IG.

[redacted]

- Part 2: All TFLs will be presented by the treatment dosing schedule.
- Part 3: If done, the presentation of TFLs will be similar to Part 1; however, if the indications selected from Part 1 do not have categories, then the Part 3 summaries may be consolidated with Part 2 for condensed CSR reporting.

Japanese safety run-in study

The data from this study is planned to be reported in the CSR separately from the Phase II study regardless of the Japanese patients' participation in the latter. However, for the brevity of CSR reporting, if deemed necessary, its reporting may be consolidated with safety reporting of Part 2. The efficacy data from this cohort will not be summarized but only listed.

Note: In a scenario that the results from part2, part 3 or the Japanese safety run-in are presented consolidatively and sorting on output data is involved for better interpretation of the results (e.g., AE summaries), then the results will be presented by study parts (part2, part 3, Japanese safety run-in) within the same output to have their own independent sorting.

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

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e., n, mean, standard deviation, median, interquartile range (Q1-Q3), minimum, and maximum) by 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.

2.1.1 General definitions

2.1.1.1 Investigational drug and study treatment

For this study, the investigational drugs are NIR178 and PDR001, each also referred as 'study drug'. When administered solely, it will be referred as 'single agent'.The study treatment is defined as NIR178 in combination with PDR001, also termed as 'combination treatment'. They will be administered in the following dose strengths and forms:

Table 2-11 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

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

The date of first (last) administration of a study drug is defined as the first (last) date when a non-zero dose of a drug is administered and recorded on the treatment page eCRF. The date of first/last administration of study drug will also be referred as start/end date of study drug.

The date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of either component of the treatment (NIR178 or PDR001) was administered and recorded on the DAR eCRF.

2.1.1.3 Study day

The study day represents the number of days elapsed since the study treatment start date including the day of treatment. It will be calculated as: study day = study date - treatment start date + 1, where study date could be an event onset date, assessment date etc. The first day of study treatment is therefore, study day 1. Example: if start of study treatment is on 05-Jan-2014 and start date of an adverse event is on 09-Jan-2014 then the study day of the adverse event onset is 5.

However, for study dates before the treatment start date, the study day is negative and derived by study day = study date - treatment start date. For example: if start of study treatment is on 05-Jan-2014 and date of lab measurement is on 02-Jan-2014 then the study day of the laboratory

abnormality is -3. Note, the day of start of study treatment is day 1, and the day before the date of first study treatment is day – 1, not day 0.

2.1.1.4 Baseline

Baseline is the result of an investigation describing the "true" state of the patient before start of study treatment administration.

For **safety evaluations**, the last available assessment on or before the date of start of study treatment for all three parts. In case time of assessment and time of treatment start is captured (e.g. pre-dose ECG), the last available assessment before the treatment start date/time is used for baseline.

For safety parameters (e.g. ECGs or vital signs), where study requires multiple replicates per time point, the average of these measurements would be calculated for baseline (if not already available in the database).

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

If patients have no value as defined above, the baseline result will be missing.

2.1.1.5 On-treatment assessment/event and observation periods

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

pre-treatment period: from day of patient's first informed consent to the day before first administration of study treatment

on-treatment period: from date of first administration of study treatment to 30 days after date of last actual administration of study treatment (including start and stop date). This period constitutes ***safety follow-up*** on all patients for 30 days after the last administration of study treatment.

post-treatment period: starting at day 31 after the last administration of study treatment. This period will constitute the following follow-up periods:

- ***extended safety follow-up period:*** all patients receiving PDR001 will continue to have safety evaluations for 150 days after the last dose of PDR001 or 30 days after the last dose of NIR178, whichever occurs later.
- ***disease progression follow-up period:*** Patients who discontinue study treatment for any reason other than death, disease progression per confirmed iRECIST or per Cheson (for DLBCL) or per PCWG3 guidance (for mCRPC) while on treatment, clinical deterioration or clinical progression, lost to follow-up, consent withdrawal or study termination, will have 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.

- ***survival follow-up period:*** 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 every 12 weeks until any of the following events(whichever occurs first): death, withdrawal of consent, loss to follow-up or at least 24 months from the first dose of study treatment.

Patients enrolled to another clinical study or alternate treatment (Protocol Section 4.3) will not have follow-up for safety, disease progression and survival assessments performed.

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

2.2 Analysis sets

A patient is considered to be enrolled into the study if he/or she has signed informed consent. Only a patient who has signed informed consent will be included in the analysis data sets.

In addition, 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.

2.2.1 Full analysis set

For the Phase II - Part 1 and Part 3 and for the Japanese safety run-in 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, which is the assigned treatment.

For Part 2 of the study, the FAS comprises all patients randomized to a study treatment, which in this case is treatment dosing schedule. According to the intent to treat (ITT) principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Unless otherwise specified, misrandomized patients (misrandomized in the interactive response technology (IRT) system) will be excluded from the full analysis set. Misrandomized patients include patients who are screen-failures, but have been randomized by the investigator before eligibility was finally assessed, however have not been treated. If patients were re-screened and successfully randomized, they will be included in the randomized set according to the dosing schedule treatment assigned in the last randomization.

The FAS will be used for all listings of raw data. Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

2.2.2 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.

2.2.3 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:

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

2.2.4 Immunogenicity analysis set

The immunogenicity (IG) set includes two parts: IG prevalence set and IG incidence set:

- The IG prevalence set includes all patients in the Safety set with a non-missing baseline ADA sample or at least one non-missing post-baseline ADA sample.
- The IG incidence set includes all patients in the Immunogenicity prevalence set with a non-missing baseline ADA sample and at least one non-missing post-baseline ADA sample.

Note that the two datasets are specific to a study drug (in this study, only PDR001) with ADA sample drawn to detect monoclonal antibodies specific to that drug.

2.2.5 PK/ECG Analysis Set

The PK/ECG analysis set includes all patients who provide baseline ECG data and at least one post-dose matched PK-ECG record (as defined in Section 5.6). Any PK-ECG analyses will be based on the PK/ECG analysis set.

2.2.6 Patient Classification

Patients may be excluded from the analysis populations defined above based on the protocol deviations (PD) entered in the database and/or on specific patient classification rules defined in Table 2-2.

Table 2-2 Patient classification based on PDs and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
Full analysis set	No written informed consent Mis-randomized patients as defined in Section 2.2.1	Patients who did not receive at least one dose of NIR178 or PDR001
Safety set	No written inform consent	Patient who did not receive at least one dose of NIR178 or PDR001 or did not have at least one valid post-baseline safety assessment.
PK Analysis Set	See definition of PK set	Patient who did not have at least one evaluable PK data for NIR178 or PDR001
IG Prevalence Set	No written informed consent	Patient did not have a non-missing baseline IG sample or at least one non-missing post-baseline IG sample
IG Incidence Set	No written informed consent	Patient did not have a non-missing baseline IG sample and at least one non-missing post-baseline IG sample
PK/ECG analysis set	See definition of PK/ECG set	Patient who did not have at least one post-dose matched PK-ECG record

2.2.7 Withdrawal of Informed Consent

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

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

2.2.8 Subgroup of interest

Given the known correlation between PD-L1 expression and response to PD-1 inhibitors in NSCLC, the dosing schedule groups will be analyzed for their post-treatment response rate based on their baseline PD-L1 expression (present/absent), as defined by expression levels <1% or > 1% by immunohistochemistry (IHC) in part 2 of this study.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment group and for all patients and listings will be reported by treatment group, both following the general analysis conventions defined under Section 2.1. No inferential statistics will be provided.

2.3.1 Patient disposition

The number (%) of treated (Part 1 and Part 3) /randomized (Part 2) patients, who are still on treatment, who discontinued the study phases, and the reason for discontinuation will be presented. The screened and not-randomized/not-treated patients and the reasons for screening failure will be listed.

For patient disposition the following summaries, when applicable, will be provided:

- Number (%) of patients who were treated/randomized*;*
- Number (%) of patients who were not treated / were randomized but not treated;
- Primary reason for not being treated*;*
- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Phase' page not completed);
- Number (%) of patients who discontinued the study treatment phase;
- Primary reason for study treatment phase discontinuation;
- Number (%) of patients who have entered the post-treatment follow-up;
- Number (%) of patients who have discontinued from the post-treatment follow-up;
- Reasons for discontinuation from the post-treatment follow-up;
- Number (%) of patients who have entered the survival follow-up.

2.3.2 Demographics and other baseline characteristics

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g., gender, age groups: 18- < 65, ≥65 years, race, ethnicity, ECOG performance status, smoking history, others as applicable) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g., age, weight, height, body surface area, body mass index) will be summarized by descriptive statistics (N, mean, median, Q1, Q3, standard deviation, minimum and maximum).

BMI and BSA are calculated using the following formulas:

- BMI [kg/m2] = weight[kg] / (height[m]**2)
- BSA [m2] = 234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000

Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include primary site of cancer, details of tumor histology/cytology, histologic grade, stage at initial diagnosis, time (in months) since initial diagnosis of primary site, time (in months) from initial diagnosis to first recurrence/progression, time (in months) since most recent relapse/progression, current extent of disease (metastatic sites).

Medical history

A listing of medical history and current medical conditions will be provided by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting.

Protocol deviations

The number (%) of patients with any protocol deviation will be tabulated by deviation category (as specified in the study Edit Check Specifications). All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized and listed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The safety set will be used for all summaries and listings of study treatment, the reporting of which will be in accordance to the general analysis conventions defined under Section 2.1 for safety.

Duration of exposure in days, actual cumulative dose, dose intensity (DI), and relative dose intensity (RDI) will be summarized by treatment group, separately for each component of study treatment (NIR178 and PDR001). Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by treatment group.

Patient-level listings of all administered treatment doses with change reasons will be produced.

2.4.1.1 Duration of exposure to study treatment

Duration of exposure (DoE) to study treatment is considered by taking into account the duration of exposure to the investigational or control drug and any combination partner, if applicable:

Duration of exposure to study treatment (*days*) = (last date of exposure to study treatment) – (start date of study treatment) + 1.

Duration of exposure to study drug (*days*) = (last date of exposure to study drug) – (start date of study drug) + 1.

The start/end dates of study drug and study treatment are defined in Section 2.1.1.2.

Part 1, Part 2 and Part 3 (if done):

The last date of exposure to study drug (NIR178 or PDR001) is defined as the end date of that drug + X, where X for a study drug with
- cyclic administration, is *(cycle length - # planned treatment days in a cycle)*
- daily administration, is zero.

Thus (see Table 2-3 for examples),

- For NIR178 continuous BID dosing, the last date of exposure is defined as the last date of administration.
- For PDR001 Q4W dosing, the last date of exposure is defined as the last date of administration + 27 days.
- For NIR178 intermittent regimens in a 28-day cycle with:
  - 2wk-on/2wk-off BID dosing, the last date of exposure is defined as the last date of administration + 14 days.
  - 1wk-on/1wk-off BID dosing (effectively 14-day sub-cycle), the last date of exposure is defined as the last date of administration + 7 days.

The last date of exposure to study treatment is defined as the latest of the last date of exposure for study drugs in the combination.

Note: If the patient died or was lost to follow-up before the derived last date, the last date of exposure to investigational drug is the date of death or the date of last contact, respectively. If the derived last date of exposure goes beyond the data cutoff date, it should be truncated to the date of data cutoff.

Table 2-3 Definition of last date of exposure of study drug

Scenario	Definition of last date of exposure of study drug	Example
Scenario 1: Study drug with a cyclic administration	The planned end date of the last cycle in which the last non-zero dose of the investigational drug was last administered. *Date of last administration of study treatment in the last cycle + (cycle length - # planned treatment days in a cylce)*	**Example 1**: In a once a week administration the cycle length is 7 days. The last date of exposure is the date of last administration in the last cycle + 6 days. **Example 2**: In a 1 week on and 3 weeks off administration the cycle length is 28 days. The last day of exposure is the date of last administration in the last cycle + 21 days. **Example 3**: In a 2 weeks on and 2 weeks off administration the cycle length is 28 days. The last day of exposure is the date of last administration in the last cycle + 14 days.

		Example 4: For an every 2 weeks administration (Q2W) the cycle length is 14 days. The last date of exposure is the date of last administration in the last cycle + 13 days. **Example 5**: In a 21-day cycle with one or several infusions in the beginning of the cycle, the last date of exposure is the date of last infusion in the last cycle + 20 days.
Scenario 2: Daily administration of the study drug, i.e. BID, QD, and every other day (This includes other intermittent treatment regimens with drug holidays to manage toxicities e.g., 3 weeks on/1 week off, 5 days on/2 days off)	*Date of last administration of a non - zero dose of the study drug.*	**Example 6**: A patient had a permanent discontinuation of the study drug 06Jan2021 after being put on a temporary interruption since 01Jan2021. In this case the last date of exposure is 31Dec2020. **Example 7**: In a 3 week on and 1 week off administration of a small molecule compound the last date of exposure is the last day of administration of a non-zero dose. **Example 8**: In a 5 days on and 2 days off administration of a small molecule compound the last date of exposure is the last day of administration of a non-zero dose.

Summaries of duration of exposure of study drugs and study treatment, expressed in weeks (DoE(days)/7) will include categorical summaries (based on clinically meaningful time intervals) and continuous summaries (i.e. mean, standard deviation etc.).

2.4.1.2 Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of study drug administration. The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the patient is on the study treatment as documented in the treatment page eCRF.

For patients who did not take any drug the cumulative dose is by definition equal to zero.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For intermittent dosing, the actual cumulative dose should be defined based on the days when the patient is assumed to have taken a non-zero dose during dosing periods. For eg., if a patient's duration of exposure is 31 days with assigned dose (X mg, BID) 2wk-on/2wk-off in 28-days dosing period, then the actual cumulative dose is the total dose administered (includes zero or reduced doses) during the initial 14 days of cycle 1 (ceiling of 31/28 = 1 complete cycle = 2 wk of dosing) and initial 3 days of cycle 2 (min(3,14) = 3). However, the planned cumulative dose is the planned dose for that patient (constant Y mg) cumulated over the dosing days within the duration of exposure.

As the study treatment is a combination agent, there might be patients in the safety set who did not take one component of study treatment and the cumulative dose for that component would be zero.

2.4.1.3 Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (*mg / day*) = Actual Cumulative dose (*mg*) / Duration of exposure to study treatment (*day*).

If for example the dosing unit is mg and the unit of time is a day:

DI (mg/day) = Actual Cumulative dose (mg) / Duration of exposure (day)
= 1200 (mg) / 18 (Day) = 66.7 (mg/day)

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (*mg / day*) = Planned Cumulative dose (*mg*) / Duration of exposure (*day*).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (*mg / day*) / PDI (*mg / day*).

DI and RDI will be summarized separately for each component of the study treatment by using their respective duration of exposure. For the purposes of reporting, DI and PDI for PDR001 will be expressed in the unit, mg/4week = mg/28 days; whereas, for NIR178, they will continue to be expressed in mg/day. Summary of RDI will include categorical summaries. The RDI categories are < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1.

The duration considered for the derivation of the DI and the RDI will be derived from the start date of study treatment to the end of the last cycle initiated, irrespective of date of death, last contact date for withdraw consent and cut-off date.

2.4.1.4 Dose reductions, interruptions or permanent discontinuations

The number of patients who have dose reductions, permanent discontinuations, or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

'Dose interrupted', and 'Dose permanently discontinued' fields will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either a 'change in prescribed dose level' or an 'error'. For the latter, actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption are entered on consecutive days with different reasons, these interruptions will be counted as separate. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Dose reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Only dose change is collected in the eCRF. Number of reductions will be derived programmatically based on the change and the direction of the change.

Dose interruption: Actual dose administered equal to zero, between the first and last non-zero doses, following a non-zero actual dose administered. Dose interruption is collected as such in the treatment page eCRF. Number of dose interruptions and corresponding reason will be summarized. A patient with continued interruptions and no return will be considered as a permanent discontinuation.

Missing data: If dose is recorded but regimen is missing or entered as 'none', it is assumed that the investigational drug was taken as per-protocol.

In some cases the total dose administered may not be the same as the total prescribed dose - for example when the dose is prescribed by BSA (mg/m2) even though the total dose administered in (mg). In such cases there may be variations in the administered dose due to variations in BSA.

2.4.1.5 Compliance

Compliance to the study treatment will be summarized in terms of the RDI or percentage of patients who took a predefined percentage of the number of prescribed doses. The predefined RDI categories are < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients falling in each category will be presented.

2.4.2 Prior, concomitant and post therapies

Summaries and listings of prior and post treatment anti-neoplastic treatments will be presented by treatment group and overall, using the FAS following the general analysis conventions defined under Section 2.1.

Prior anti-neoplastic therapy

The number (%) of patients who received any prior anti-neoplastic medication will be summarized and listed. The summary of prior anti-neoplastic medications may include the total number of regimens (note: there can be more than one medication per regimen), setting at last medication, time (in days) from last treatment to progression, best (hematological/cytogenetic/molecular) response at last treatment (defined to be the best response during the last treatment regimens recorded), duration (in months) of last response (last response is the response at last medication) and reason for discontinuation at last medication. The last medication is defined based on the last start date of all prior regimen components. Prior anti-neoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class and preferred term (PT).

The summary and listing of prior anti-neoplastic surgery may include prior surgery, procedure at last surgery, and residual disease at last surgery.

The summary and listing of prior anti-neoplastic radiotherapy may include the radiotherapy locations (including all locations recorded for each patient), setting at last radiotherapy, and whether last radiotherapy was 30% of bone marrow.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

Post treatment anti-neoplastic therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed by ATC and PT.

Concomitant medications

Concomitant therapy is defined as any intervention (therapeutic treatment and procedure) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy includes medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment. Concomitant medications will be coded using the WHO Drug Reference Listing (DRL) dictionary that employs the WHO ATC classification system.

All concomitant therapies and significant non-drug therapies will be summarized and listed using the safety set. Any concomitant therapies and significant non-drug therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

2.5 Analysis supporting primary objective(s)

There are three parts in 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 the efficacy of 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 treatment indications based on the emerging data from part 1 and part 2.

The reporting of efficacy analyses for respective parts will follow the general analysis conventions defined under Section 2.1.

2.5.1 Primary endpoint(s)

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 (see Protocol Appendix 2 for details) for solid tumors, Cheson et al (2014) for DLBCL, or PCWG3 criteria for mCRPC (see Protocol Appendix 5 for details).

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.2.1 Part 1

This part will contain thirteen groups: (1) RCC IO naive at NIR178 160 mg BID, (2) RCC IO naive at NIR178 240 mg BID, (3) RCC IO pretreated at NIR178 240 mg BID, (4) pancreatic cancer at NIR178 160 mg BID, (5) urothelial cancer at NIR178 160 mg BID, (6) HNSCC IO naive at NIR178 160 mg BID, (7) HNSCC IO pretreated NIR178 160 mg BID, (8) MSS CRC RAS wildtype NIR178 160 mg BID, (9) MSS CRC RAS mutant NIR178 160 mg BID, (10) TNBC at NIR178 160 mg BID (11) melanoma IO pretreated NIR178 160 mg BID, (12) DLBCL at NIR178 160 mg BID, and (13) and mCPRC at NIR178 240 mg BID.

Note: The efficacy data from the Non-HNSCC patients, MSS CRC patients with unknown RAS status and melanoma IO naive patients will not be included in the statistical model. The efficacy data from any new treatment indications added to the existing 13 groups before the study closure (as a consequence of Protocol Amendment 5) that qualify the criteria for Part 1 may be used to inform the model.

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 each and across treatment indications. 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 treatment indications
- Scenario B: ORR is similar for some treatment indications and different in others
- Scenario C: The various treatment indications have distinct ORR

The pre-specified analysis is adaptive in the sense that when response is similar across all treatment indications (Scenario A), then it borrows information from across all the various treatment indications. In cases when few of the treatment indications have similar ORR (Scenario B), the model provides more precise estimates of ORR rates for the treatment indications that have similar response rates by allowing to borrow information only across these treatment indications. In the other possibility when the various treatment indications have distinct anti-tumor activity (Scenario C), the design allows little/no borrowing of information across treatment indications. 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 treatment indication j (= 1,…, J=13). For each treatment indication 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 few of the treatment indications, 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, account for the case where a few treatment indications show no efficacy and others are promising. Thus, for each treatment indication 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) 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, and the prior distributions for μ_1, τ_1, μ_2, and τ_2, see Protocol 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 treatment indication 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 2-4) (i.e. posterior mean ORR >= C2)
b. Posterior probability of "not being clinically meaningful" (column for C1 in Table 2-4) is less than 10% (i.e., prob(ORR <= C1|data) < 10%)

Table 2-4 Type of tumors of interest with definition of being clinically meaningful

Serial no.	Disease Code	Treatment indication	Not Clinically meaningful (C_1)	Clinically meaningful (C_2)
1	T5	RCC naive at 160 mg[e]	<= 25%	>= 37%
2	T12	RCC naive at 240 mg[e]	<= 25%	>= 37%
3	T11	RCC pretreated at 240 mg[e]	<= 10%	>= 20%
4	T2	Pancreatic[b]	<= 8%	>= 16%
5	T4	Urothelial[d]	<= 15%	>= 27%
6	T3	HNSCC naive[c]	<= 13%	>= 23%
7	T8	HNSCC pretreated[c]	<= 5%	>= 13%
8	T9	MSS CRC – RAS wildtype[h]	<= 5%	>= 13%
9	T10	MSS CRC – RAS mutant[h]	<= 5%	>= 13%
10	T6	TNBC[f]	<= 5%	>= 13%
11	T7	Melanoma pretreated[g]	<= 10%	>= 25%
12	T1	DLBCL[a]	<= 10%	>= 20%
13	T13	mCRPC at 240 mg[i]	<= 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, T10 and T12, no interim analysis will be done). Extend recruitment of up to 30 patients in each treatment indication 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. Goodman (2015) g. Hodi et al (2016) h. Le et al (2015) . i. Bendell et al (2019)				

Details of statistical methodology :

This section provides the details of model for Part 1 of the study. Prior specifications of model parameters are provided in detail. Data analysis and decision making in real trial are illustrated using hypothetical data scenarios, see Protocol Appendix 4.

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 are described in this section.

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

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

This yields $V_{\mu 1} = 7.843 – 0.25^2 = 7.781$ ($\approx 2.789^2$) and $V_{\mu 2} = 4.167 – 0.25^2 = 4.104$ ($\approx 2.026^2$).

This allows a considerable uncertainty on prior belief of θ.

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.

Specification of mixture weights (p_j)

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

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

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.

2.5.2.2 Part 2

Different schedules of NIR178 160 mg BID in combination with PDR001 in NSCLC will be evaluated for efficacy using ORR as the primary endpoint. 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.

The probability that one schedule is greater than another schedule given the data will be provided:

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

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

2.5.2.3 Part 3

As of Protocol Amendment 6, TNBC is one of the selected treatment indications in Part 3. A second treatment indication may be considered for Part 3 after completion of Part 1. Separately from Part 1 TNBC patients (since the inclusion/exclusion criteria are different), the patients in Part 3 who will receive the new FCT formulation of NIR178 160 mg continuous dosing in combination with PDR001 will be analyzed for efficacy by treatment group using ORR as a primary endpoint with efficacy intervals as reported in Table 2-4 for the TNBC group.

ORR will be provided 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

2.5.3 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 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.

2.5.4 Sensitivity analyses

Not applicable.

[redacted]

2.6 Analysis supporting secondary objectives

2.6.1 Efficacy objectives

The secondary objective is to assess the efficacy of NIR178 in combination of PDR001 using ORR per iRECIST, and other efficacy measures including disease control rate (DCR), duration of response (DOR), progression free survival (PFS) and 2 year overall survival (OS) by both RECIST v1.1 and iRECIST for solid tumors, by PCWG3 guidance (see Protocol Appendix 5) for mCRPC, and by Cheson et al (2014) for DLBCL.

These efficacy endpoints will be summarized for all the treatment groups contributing to the analysis of primary efficacy objective (see Section 2.1 general analysis conventions).

ORR:

Overall response rate (ORR) is defined as the proportion of patients with best overall response (BOR) of immuno-related complete response (iCR) or immuno-related partial response (iPR), as per local review and according to iRECIST (see Protocol Appendix 3 for details) for solid tumors.

ORR as per iRECIST will be provided for each treatment indication along with corresponding 95% confidence interval (CI).

DCR:

DCR is the proportion of patients with a best overall response of CR, PR or stable disease (SD). DCR will be summarized by treatment indication with accompanying 95% confidence intervals.

OS, PFS and DOR:

OS is defined as the time from date of start of treatment to date of death due to any cause. If a patient is not known to have died, OS time will be censored at the date of last contact. The 2 year OS rate is the proportion of patients with at least 2 years of OS.

PFS is defined as the time from start of treatment date to date of the first documented disease progression or date of death, whichever happens first. If a patient has not had the event at the date of analysis cut-off, PFS will be censored at the time of the adquate tumor assessment before the cut-off.

For patients with a confirmed CR or confirmed PR, the DoR is the time from date of first documented response (CR or PR) to date of first documented progression or death due to underlying cancer, whichever happens first. If progression or death has not occurred at the date of analysis cut-off, then DoR will be censored at the date of last adequate tumor assessment before the cut-off.

Kaplan-Meier (KM) plots and estimates for time-to-event endpoints including OS, PFS, and DOR will be presented for treatment groups of size ≥10 patients with estimable median. Median with accompanying 90% confidence intervals along with KM estimates for PFS and OS at 4, 6, 9, 12, 18 and 24 months will be reported.

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 (≥ 10) patients.

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 melanoma IO naive 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 using estimable endpoints (enough patients for the endpoints to be estimated); otherwise, the efficacy data will be listed.

2.6.2 Safety objectives

All safety analyses will be based on the safety set (see Section 2.2.2), which will be used for presenting summaries and listings by treatment groups and overall patients following the general analysis conventions defined under Section 2.1.

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

All safety reporting will be based on observation periods defined in Section 2.1.1.5.

Safety summaries (tables, figures) will primarily be based on all data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. Following the last administration of study treatment, adverse events (including serious adverse events), and new antineoplastic therapies will be 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 Protocol Section 10.5.2.2).

2.6.2.1 Adverse events (AEs)

Summary tables for adverse events (AEs) will include AEs that started or worsened during the on-treatment period, also termed as treatment-emergent AEs.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary SOC and for each PT. AEs will be coded using the MedDRA and assessed according to the CTCAE version 4.03, respectively. The latest available MedDRA version at the time of the analyses should be used. The MedDRA and CTCAE version used should be specified in the footnote of relevant tables.

A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables. In AE summaries, the primary SOC will be presented alphabetically, and the PTs will be sorted within primary SOC in descending frequency. The sort order of the PTs will be based on their frequency in the most relevant group.

Note: In AE summaries with consolidated study parts, AEs will be presented by study parts, with each part having its own sort order (see General analysis conventions under Section 2.1 for detail).

The following AE summaries will be produced:

- Overview of adverse events (number and % of patients with any AE, any SAE, any fatal SAEs, any AE with dose reductions/interruptions/discontinuations, and correspondingly, with treatment-related AEs; also, AEs requiring additional therapy);
- AEs regardless of study drug relationship by SOC and/or PT, and severity;
- AEs suspected to be study drug related by SOC and/or PT, and severity;
- AEs leading to dose interruption/adjustment regardless of study drug relationship, by SOC and/or PT, and severity;

- AEs leading to dose interruption/adjustment suspected to be study drug related, by SOC and/or PT, and severity;
- AEs leading to study drug discontinuation regardless of study drug relationship by SOC and/or PT, and severity;
- AEs leading to study drug discontinuation suspected to be study drug related by SOC and/or PT, and severity;
- SAEs regardless of study drug relationship by SOC and/or PT, and severity;
- SAEs suspected to be study drug related by SOC and/or PT, and severity;

All AEs collected on the AE eCRF page will be listed with the information collected on those AEs e.g. AE relationship to study drug, AE outcome, etc. AEs with start date in the post-treatment period will be flagged in the listings; those that start in the pre-treatment period will be identified by study day prefixed with a '-' (a negative sign). Additionally, listings for AEs and SAEs on screened patients who are not treated will be provided with information on those AEs including start-end dates, outcome etc.

2.6.2.2 Adverse events of special interest (AESI) / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compounds PDR001 or NIR178. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

The reporting of AESIs will follow similar conventions as used for AEs (see General analysis conventions in Section 2.1).

Given that only PDR001 specific electronic Case Retrieval Strategy (eCRS) exists, summaries of AESI associated with the combination (NIR178 + PDR001) will be reported using PDR001 specific eCRS for the combination arm by treatment groups. For each specified AESI, number (%) of patients with at least one event of the AESI occurring during on-treatment period will be summarized together with the individual preferred terms in that grouping. In addition, number (%) of patients with at least one AESIs by maximum CTC grade will be summarized.

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

2.6.2.3 Deaths

Separate summaries for on-treatment and post-treatment deaths will be produced by SOC and PT.

All deaths will be listed and post-treatment deaths will be flagged. A separate listing of deaths prior to the treatment initiation will be provided for all screened patients.

Note: "Study indication" as primary reason of death should be coded using MedDRA terms based on the diagnosis eCRF field at start of study. If not coded accordingly in the database, it still must be included in the summary table. Coded reasons for deaths will then be summarized by category 'Study indication' and 'Other' (as selected by the investigator).

The death summaries cover patients from the safety set. The count of deaths reported in safety analyses may differ from that reported in the efficacy analyses.

2.6.2.4 EudraCT and clinicaltrials.gov requirements for AEs and Death summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two tables (listed below) must be produced for treatment-emergent safety events (AEs/SAEs and deaths) that occurred for **150 days** after the last dose of PDR001 or 30 days after the last dose of NIR178, whichever occured later.

1. Deaths and serious adverse events, by system organ class and preferred term.
2. Non-serious AEs regardless of study drug relationship, with an incidence rate greater than 5% by SOC and PT.

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

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

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

The presence of at least one SAE / SAE suspected to be study drug related / non SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

At the time of xml preparation, a single file per registry (i.e., 1 file for EudraCT and 1 file for CT.gov). with all reporting groups in the study will need to be submitted to the CDO.

2.6.2.5 Laboratory data

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.

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 produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline;
- Shift tables using CTC grades to compare baseline to the worst on-treatment value;
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value;

The following listing(s) will be produced for the laboratory data:

- Listing of all CTC grade 3 or 4 laboratory toxicities.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST, and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN *(potential Hy's law)*

Potential Hy's Law events are defined as those patients with concurrent occurrence of AST or ALT > 3xULN and TBL > 2xULN and ALP < 2xULN in the same assessment sample during the on-treatment period. Further medical review should be conducted to assess potential confounding factor such as, liver metastases, liver function at baseline etc.

For more details and adaptation of above summary, Oncology Hepatic Safety guidance should be referred.

2.6.2.6 Other safety data

2.6.2.6.1 ECG and cardiac imaging data

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

12-lead ECGs including PR, QRS, QT, QTcF, QTcB, and RR intervals will be obtained centrally/locally for each patient during the study. ECG data will be read and interpreted centrally/locally.

The following summaries will be presented:

- Change from baseline for ECG parameters by timepoint
- Number and percentage of patients with notable ECG values.
  - QT, QTcF, or QTcB
    - New value of > 450 and ≤ 480 ms
    - New value of > 480 and ≤ 500 ms
    - New value of > 500 ms
    - Increase from baseline of > 30 ms to ≤ 60 ms
    - Increase from baseline of > 60 ms
  - HR
    - Increase from baseline >25% and to a new HR > 100 bpm
    - Decrease from baseline >25% and to a new HR < 50 bpm
  - PR
    - Increase from baseline >25% and to a new PR > 200 ms
    - New PR > 200 ms
  - QRS
    - Increase from baseline >25% and to a new QRS > 120 ms
    - New QRS > 120 ms

A listing of patients with only notable ECG values will be produced. For patients with at least one notable ECG parameter value, all parameters should be listed.

PK-ECG analysis

A linear mixed effects model will be used to analyze QTcF change from baseline versus plasma NIR178 concentration using the PK/ECG analysis set. The linear mixed effects model is as follows:

$$\Delta\text{QTcF}_{ij} = (\beta_0 + b_{0i}) + \beta_1 baseline\_QTcF_i + \beta_2 concentration_{ij} + \epsilon_{ij}$$

In this model, b_{0i} is the patient's random effect. A compound symmetry covariance structure is assumed; other covariance structures may be explored.

The estimated mean QTcF change from baseline will be presented along with the two-sided 90% CI for different concentration thresholds (mean, Q1, median, and Q3) of Cmax for dose levels 160mg BID and 240 mg BID, corresponding to C1D1 and/or steady state.

- These thresholds will be determined from C1D1 and/or steady state Cmax
- Baseline QTcF will be set to its median baseline value

QTcF is suggested by the ICH E14 guidance (attached at the end of this document (Section 6)) and is more accurate than other correction methods in patients with altered heart rates. [redacted]

A check of mean concentration versus time and mean QTcF change from baseline versus time should be performed to rule out any delayed effect (hysteresis). [redacted]

2.6.2.6.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters will be collected: weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

The number and percentage of patients with on-treatment notable vital sign values (high/low) will be presented.

A listing of patients with only notable vital sign values will be produced. For patients with at least one notable vital sign parameter value, all parameters should be listed.

For analysis of vital signs, the clinically notable vital sign criteria are provided in Table 2-5 below.

Table 2-5 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	below normal value
Weight (kg)	increase ≥10% from baseline	decrease ≥10% from baseline
Systolic blood pressure (mmHg)	≥180 with increase from baseline of ≥20	≤90 with decrease from baseline of ≥20
Diastolic blood pressure (mmHg)	≥105 with increase from baseline of ≥15	≤50 with decrease from baseline of ≥15
Pulse rate (bpm)	≥100 with increase from baseline of >25%	≤50 with decrease from baseline of > 25%
Body temperature (°C)	≥ 39.1	-

2.6.2.6.3 Additional analyses

Tolerability of study drug treatment will be based on the safety set and assessed by summarizing the number of treatment dose interruptions and dose reductions by part. Reasons for dose interruption and dose reductions will be listed and summarized. Cumulative dose, DI and RDI of each study drug will be summarized by treatment group (for reporting and definitions, see Section 2.1 and Section 2.4.1).

For Japanese safety run-in study, frequency, severity and seriousness of dose limiting toxicities, AEs, laboratory abnormalities and other safety parameters (ECG, physical exams etc) will be summarized separately from the Phase II study or in a consolidated setting using safety set (see General analysis conventions in Section 2.1).

2.6.3 Pharmacokinetic endpoints

Pharmacokinetics of the study drugs will be assessed to support a secondary objective using the PK datasets and will be reported by treatment groups following the general analysis conventions used for the safety set (see Section 2.1).

PK parameters

PK parameters such as those listed in in Table 2-6 will be estimated and reported, when applicable. The PK parameters are derived based on non-compartmental methods for NIR178 and its metabolite NJI765 and PDR001.

Table 2-6 Non-compartmental PK parameters

AUCinf	The AUC from time zero to infinity (ng*hr*mL-1)
AUClast	The AUC from time zero to the last measurable plasma concentration sampling time (tlast) (ng*hr*mL-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 concentration following a single dose administration (ng/mL)
Tmax	The time to reach maximum (peak) plasma concentration following a single dose administration (hr)
T1/2	The elimination half-life associated with the terminal slope (□z) of a semi logarithmic concentration-time curve (hr).
[1]CL/F	The total apparent body clearance of drug (L*hr-1)
[1]Vz/F	The apparent volume of distribution during terminal phase (associated with □z) (L)

[1] For parent drug only

Descriptive statistics (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum, and maximum) will be presented by treatment groups using the

PAS for all PK parameters defined in Table 2-6 except Tmax, where only n, median, minimum, and maximum will be presented.

For NJI765, CL/F, Vz/F and elimination half-life will not be reported.

PK parameters estimated for the Japanese patients in Japanese safety run-in study may be reported consolidatively with rest of the Phase II study patients.

All individual PK parameters will be listed by treatment using the safety set.

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum, and maximum) for NIR178, NJI765, and PDR001 concentration will be presented at each scheduled timepoint by treatment using the PAS.

Individual concentration-time profiles for NIR178, NJI765, and PDR001 concentrations with median will be displayed graphically by treatment using the safety set on the semi-log view. In addition, the mean (+/- SD) concentration-time profiles for NIR178, NJI765, and PDR001 by treatment over time will be displayed graphically using the PAS on the linear and semi-log view.

PK plasma concentration time profiles of Japanese patients in Japanese safety run-in study will be reported separately from Phase II study patients.

All individual plasma NIR178, NJI765, and PDR001 concentration data will be listed by treatment using the safety set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the Bioanalyst and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

At the time of analysis, concentration data from patients may be removed from the estimation of certain PK parameters depending on the number of available blood samples, concomitant medications, vomiting, etc. Reason(s) for removing concentration data will be provided. Specific timepoints might be removed from the analysis set if technical issues with the sample are reported (e.g., sampling issues, missing information). These patients and concentration data points will be identified at the time of analysis.

2.6.4 PD and PK/PD analyses

Not applicable.

2.6.5 Immunogenicity

Immunogenicity of PDR001 will be assessed to support a secondary objective using the IG datasets and will be reported by treatment groups following the general analysis conventions used for the safety set (see Section 2.1).

2.6.5.1 Sample ADA status

Each anti-drug anti-body (ADA) sample is assessed in a three tiered anti-drug anti-body (ADA) testing approach. All ADA samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not patient to a confirmatory assay. Samples testing positive in the screening assay are then patiented to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier).

Samples identified as positive in the confirmatory assay are considered ADA positive.

Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data:

- Result of assay according to pre-specified confirmatory cut point: 'POSITIVE', 'NEGATIVE', or 'NOT REPORTABLE'
- Titer: numerical representation of the magnitude of ADA response
- Threshold for determining treatment-boosted (titer fold change (i.e. x-fold))

The following definitions apply only to non-missing samples:

- ADA-negative sample: Sample where assay result is 'NEGATIVE
- ADA-positive sample: Sample where assay result is ADA positive.

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

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

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

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

Listings will be provided of ADA sample status specific to the PDR001 component of the study treatment.

2.6.5.2 Patients ADA status

Any ADA sample collected after extended follow up period of 150 days of the last dose of the drug spartalizumab will not be used for summaries or derivations and will only be included in the listing.

Patient ADA status is defined as follows:

- *Treatment-induced ADA-positive patient*: patient with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- *Treatment-boosted ADA-positive patient*: patient with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.
- *Treatment-unaffected ADA-positive patient*: patient with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample.
- *Treatment-reduced ADA-positive patient*: patient with ADA-positive sample at baseline and at least one non-missing post-baseline sample, all of which are ADA-negative samples.
- *ADA-negative patient*: patient with ADA-negative sample at baseline and at least one non-missing post-baseline sample, all of which are ADA-negative samples.
- *Inconclusive patient:* patient who does not qualify for any of the above definitions or a patient for which the baseline sample is missing.

The following summaries of ADA patient status (n and %) will be provided using Immunogenicity incidence set (for % the denominator is the number of patients in the Immunogenicity incidence set unless otherwise specified):

- Patients with ADA-negative sample at baseline
- Patients with ADA-positive sample at baseline
- ADA-negative patients: for %, the denominator is the number of patients in Immunogenicity incidence set.
- Treatment-induced ADA-positive patients; for %, the denominator is the number of patients with ADA-negative sample at baseline.
- Treatment-boosted ADA-positive patients; for %, the denominator is the number of patients with ADA-positive sample at baseline.
- Treatment-reduced ADA-positive patients; for %, the denominator is the number of patients with ADA-positive sample at baseline.

- ADA-positive patients (i.e. ADA incidence): calculated as the number of treatment-induced, treatment-boosted and treatment-reduced ADA-positive patients; for %, the denominator is the number of patients in Immunogenicity incidence set.

Listings will be provided of ADA patient status.

2.6.6 Patient-reported outcomes

Not applicable.

2.8 Interim analysis

Part 1:

Patients will be continuously accrued and the data will be analyzed using a Bayesian hierarchical model mentioned in Section 2.5.2. Interim analysis for a treatment indication will be performed when at least 10 enrolled patients have at least one post-baseline disease assessment. Note: As of Protocol Amendment 6, the groups, RCC IO naïve (NIR178 240 mg BID) and MSS-CRC, were extension of the earlier cohorts - the former had new patients enrolled at 240 mg as a result of Protocol Amendment 5; and, the latter was split in two groups, RAS wild type and RAS mutant, with 20 patients each upon decision to expand enrollment at their respective IA.

The futility analysis will not be binding. At each of these analyses, the current (posterior) probability that the response rate for each of the treatment indications is greater than "clinically meaningful threshold (column for C2 in Table 2-4)" will be determined.

These probabilities will be used to adapt the design. All available data for evaluable patients will be used for analysis at each interim analysis. However, a decision will be made only for the qualified treatment indication (≥ 10 patients with at least one post-baseline assessment) based on the calculated probability as given below:

1. Accrual to a treatment indication will cease for futility if it is very unlikely (posterior probability <20%) that the response rate for the treatment indication is "clinically meaningful" (≥C2 threshold in Table 2-4)
2. Otherwise, recruitment will continue until the next IA is performed or a maximum of 30 patients in that treatment indication 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.

The results at the final analysis within a treatment indication 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 study:

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 1.1.4.

3 Sample size calculation

3.1 Part 1

The design of this part is adaptive in nature; hence, the final sample size is not fixed. As of Protocol Amendment 6, a minimum of 10 and a maximum of 30 evaluable patients will have enrollment in 13 treatment indication groups (see Section 2.5.2.1). Thus, the total sample size across all treatment indications will be between 130 and 310.

Patients will be continuously accrued, and the accumulated data will be analyzed at interim as described in Section 2.8. Based upon the results of any of these analyses, enrollment into one or more treatment indications 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 Protocol Table 14-12) are provided in Protocol Appendix 4. The number of simulations generated for each scenario is 1000. For additional details, please see Protocol 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:

Protocol Table 14-13 (Scenario 1) presents the operating characteristics of the design when the true underlying ORR of none of 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 tumor type is 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%.

Protocol Table 14-14 (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 (at final analysis) for each tumor type is appropriately high, ranging between 78.2% and 90.7%. Similarly, the chances of stopping for futility at IA is 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%).

Protocol 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%).

Note:

Simulations were run after the inclusion of MSS CRC RAS mutant, MSS CRC RAS wildtype and HNSCC pretreated groups that show on-study decisions made under the model after the new groups are added (refer Protocol Section 14.4.4). The hypothetical data scenarios for interim and final analysis can be found in Protocol Table 14-16 and Protocol Table 14-17 respectively. For each scenario, the posterior probability of being “clinically meaningful” and “not clinically meaningful” (T1-T10 in Protocol Table 10-1) are calculated by group and displayed in the tables.

Similar exercise was conducted 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) (refer Protocol Section 14.4.5). The hypothetical data scenarios for interim and final analysis can be found in Protocol Table 14-18 and Protocol Table 14-19 respectively.

3.2 Part 2

At least 20 patients will be enrolled in each of the dosing schedules.

Table 3-1 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 3-1 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 3-1, 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 3-2 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.

Table 3-2 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 3-2, 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 3-3 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 3-3, 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%.

3.3 Part 3

If initiated, 20 patients will be enrolled in each group of treatment indication (max two) selected based on emerging data from Part 1 and Part 2. For the treatment indication/s 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 indication using NIR178 160 mg BID continuous dosing schedule in combination with PDR001 (see Section 1.1.3).

A sample size of 10 patients treated at FCT NIR178 160 mg BID in combination with PDR001 in TNBC indication in Part 3 provides a high probability, 77%, of observing 0 or 1 adverse event when the true incidence rate is 9% (Table 3-4).

Table 3-4 Probability of detecting adverse events with specified incidence rate based on N=10 patients

	AE incidence rate			
Number of adverse events	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 3-5 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 3-5, 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 3-5 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

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 Protocol Section 5, and who meet all other inclusion/exclusion criteria. The dose escalation strategy is detailed in Section 1.1.4.

4 Change to protocol specified analyses

The study is closed out due to lack of sufficient efficacy and there is only TNBC indication opened in Part 3 at a single dose level - NIR178 160 mg BID. The dose increment criteria of Part 3 described in Section 1.1.3 will not be evaluated as no patients are enrolled at 240mg in Part 3.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule applies to daily dosing and should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient should be treated as on-going, and the cut-off date should be used as the dose end date.

This scenario should not be applicable for final CSR. All patients should have EOT page complete before the Database lock for Final CSR.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Please note that date of assessment on EOT CRF might be very different from last date of dose.

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

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

Use Dec31yyyy

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

Use EOT date

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

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing, then end-date should not be imputed.

5.1.2 AE date imputation

A missing AE start date will be imputed using the logic matrix described in Table 5-1.

Table 5-1 Imputation rules for a partially missing AE start date

	AEM missing	AEM<TRTM	AEM=TRTM	AEM>TRTM
AEY missing	Not imputation	Not imputation	Not imputation	Not imputation
AEY<TRTY	(D)	(C)	(C)	(C)
AEY=TRTY	(B)	(C)	(B)	(A)
AEY>TRTY	(E)	(A)	(A)	(A)

AEM=Month AE started, AEY=Year AE started
TRTM=Month treatment started, TRTY=Year treatment started

Table 5-2 is the legend to the logic matrix shown in Table 5-1 and details the relationship of AE start date to study treatment start date.

Table 5-2 Imputation legend and AE/treatment start date relationship

AE start date relationship	Imputation
(A) After treatment start or uncertain	MAX(01MMMYYYY, TRTSDT+1)
(B) Uncertain	TRTSDT+1
(C) Before treatment start	15MMMYYYY
(D) Before treatment start	01JULYYYY
(E) After treatment start	01JANYYYY

Before treatment start: Partial date indicates AE start date is prior to treatment start date.
After treatment start: Partial date indicates AE start date is after treatment start date.
Uncertain: Partial date insufficient to determine relationship of AE start date to treatment start date.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to adverse events starting before or on the cut-off date and not having documented end date.

No imputation will be performed for missing/incomplete AE end dates.

5.1.3 Concomitant medication date imputation

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.1.2). For concomitant medication reports with no documented end date, medication will be reported as 'ongoing' if captured as such in the eCRF, otherwise it will be reported missing.

No imputation will be performed for concomitant medication end dates.

5.1.3.1 Prior therapies date imputation

Start date

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that scenario (B) will be replaced to be 'start date of study treatment - 1'. (see Section 5.1.2)

End date

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

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

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

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

5.1.3.2 Post therapies date imputation

Start date

Imputed date = max (End of Treatment date + 1, first day of the month), if day is missing.

Imputed date = max (End of Treatment date + 1, 01JAN), if day and month are missing.

Imputed date = End of treatment date +1, if the date is completely missing.

End date

No imputation

5.1.4 Other imputations

Diagnosis and extent of cancer

When a date is recorded as a partial date, the missing day is imputed to the 1st of the month (e.g., DEC2021 imputed to 01DEC2021) and if the day and month are both missing then to 1st of January of that year (e.g., 2021 imputed to 01JAN2021). Such imputed data will be flagged in the listings.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g., MRI scan, CT scan) must be completed with day, month, and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g., MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise, if overall response is progression the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the

importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE version 4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

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

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

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

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

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

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

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

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above.

5.4 Definition and derivation rules for iRECIST

Assessment by irRECIST

For iRECIST the key difference from RECIST in the assessment of these endpoints is the recommendation that iPD be confirmed at least 4 weeks after the criteria for iPD are first met. A single assessment of iPD followed by a subsequent assessment of iSD or better will be considered as a pseudo-progression. These are not considered as progression events for the purposes of analysis. When iPD is confirmed by a second assessment, the date of the first of these two assessments is then the date of progression. For patients who have ended treatment without a valid confirmation assessment, for the purposes of analysis the single assessment of iPD will be treated as a confirmed iPD. At time of analysis there may be patients whose last adequate assessment is an unconfirmed iRECIST progression (iUPD) but who are continuing treatment. In these cases that progression will be treated as a confirmed progression for the primary analysis, and sensitivity analysis of time-to-event endpoints may be conducted in which the patient is censored at the time of last adequate assessment.

5.4.1 Total measurable disease burden

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

5.4.1.1 Best percentage change from baseline in TMTB

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

5.4.2 Assessment of disease progression

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

5.4.2.1 Pseudo-progression

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

5.4.2.2 Confirmed progression

Confirmed progression 1 (type 1, iCPD1) is declared if a patient has 2 consecutive tumor assessments at least 4 weeks (28 days) apart, both showing disease progression. Assessments with

an iUNK response or iPD assessments <28 days after initial iPD, are discarded. The first iPD is flagged as iCPD1, while all subsequent iPDs are flagged as iXPD1.

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

Sequence of assessments	Instructions
1 iPD 2 iUNK 3 iPD (Assessment 1 + 30 days)	• Assessment 3 is ≥28 days after Assessment 1 • Assessment 3 represents confirmation of iPD at assessment 1 • Assessment 1 iPD is flagged iCPD1 • Assessment 3 iPD is flagged iXPD1
1 iSD 2 iPD 3 iPD (Assessment 2 + 20 days) 4 iPD (Assessment 2 + 30 days)	• Assessment 3 is <28 days after Assessment 2 • Assessment 4 is ≥28 days after Assessment 2 • Assessment 4 represents confirmation of iPD at assessment 2 • Assessment 2 iPD is flagged iCPD1 • Assessment 3 and 4 iPDs are flagged iXPD1

Confirmed progression 2 (type 2, iCPD2) is declared if a patient discontinues treatment following a single iPD with no subsequent assessments ≥28 days later. Assessments with an iUNK response or iPD assessments <4 weeks (28 days) after initial iPD, are discarded. Discontinuation of treatment is obtained from EOT eCRF.

The assessment is flagged as iCPD2 and subsequent iPDs (<28 days after first iPD) are flagged as iXPD2.

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

Sequence of assessments	Instructions
1 iSD 2 iPD - EOT	• Patient withdraws after initial progression (Assessment 2) without confirmation • Assessment 2 iPD is flagged as iCPD2
1 iPD 2 iPD (Assessment 1 + 20 days) - EOT	• Assessment 2 iPD is <28 days after Assessment 1, so it does not represent confirmation • However, patient has completed treatment • Assessment 1 iPD is flagged iCPD2 • Assessment 2 iPD is flagged iXPD2

5.4.2.3 Unconfirmed progression

Unconfirmed progression is applicable to patients who are continuing treatment at time of analysis cut-off, but whose last assessment showed iPD. For the primary analysis, these patients will be analyzed as though this event represents confirmed progression, however sensitivity analyses may be conducted in which these patients are censored at the time of last assessment. In later analyses, additional data will lead to iUPD events being reclassified as pPD, iCPD1, or iCPD2.

Patients with a single iPD and no assessment of iSD or better (assessment with an iUNK response or iPD assessments <4 weeks after initial iPD, are discarded) continuing treatment at the time of the analysis will be considered as unconfirmed (iUPD).

5.4.3 Best overall response

Assessment of BOR will be based on all assessments up to and including the first assessment of iPD (iCPD1, iCPD2, or iUPD). Assessments made more than 150 after EOT will be excluded.

BOR will be defined with the following hierarchy:

iCR	Two consecutive determinations of iCR ≥28 days (4 weeks) apart. Non-consecutive assessments of iCR may also result in BOR of iCR if all intervening assessments are iUNK.
iPR	Two determinations of iPR (or better) ≥28 days (4 weeks) apart. The two determinations of iPR (or better) may be separated by one or more assessments of iSD, but may not be separated by an assessment of iPD.
iSD	At least one iSD assessment (or better) >42 days (6 weeks) after start of treatment/randomization
iPD	Event flagged as iCPD1, iCPD2 or iUPD ≤84 days (12 weeks) after start of treatment/randomization
iUNK	All other cases

5.4.4 Time-to-event analyses

5.4.4.1 Progression events

iUPD should only be used for sensitivity analyses. For the primary analysis iUPD events will be treated as confirmed progression.

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

Patients are classified as follows:

0	No event (censored)
1	Confirmed iPD (iCPD1 or iCPD2)
2	Unconfirmed iPD (iUPD)

For the primary analysis of time-to-event endpoints, both confirmed and unconfirmed progression will be included as progression events with date of progression being the date of the assessment flagged as iCPD1, iCPD2, or iUPD according to the algorithm defined in Section 5.5.2.

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

5.4.4.2 Definition of start and end dates for time-to-event variables

Assessment date

Assessment date is defined as for RECIST v1.1 (CSP Appendix 2).

Start date

Start date is as defined for RECIST v1.1 (CSP Appendix 2).

End dates for time-to-event variables

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of death as recorded on death eCRF.
- Date of progression is as defined in Section 5.5.2.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of iCR, iPR, or iSD, which was made before progression or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of start of treatment/randomization is used.

Note: for sensitivity analyses of time-to-event endpoints ongoing patients with an iUPD may be censored at the time of last assessment.

5.4.4.3 Censoring reason

Censoring reason is derived as for RECIST v1.1 (CSP Appendix 2).

5.4.4.4 Duration of response

Duration of response is defined as a time interval between the first date of confirmed iCR/iPR and the date of progression as defined in Section 5.5.2. Intervening assessments of pPD are excluded from the assessment.

5.5 PK/ECG dataset preparation

5.5.1 ECG data

If QTcF change from baseline for a particular record is missing, then the record will be excluded. In specific, two scenarios will cause this exclusion: (1) if the patient does not have valid baseline ECG information, then all the records for this patient will be excluded; (2) if a patient has missing post baseline QTcF at a certain visit/timepoint, then the record for that particular visit/timepoint will be excluded.

After the aforementioned exclusions are applied, the average of replicate ECG records at each timepoint (scheduled or unscheduled) will be taken. Unscheduled ECG measurements taken within the first and last replicates at a scheduled visit (as determined by ECG date and time) will be included in this computation (if present).

The ECG date and time is the date and time associated with the average is the date and time of the single ECG record or the date and time of the first of any replicate ECG records.

The ECG data after the aforementioned processing steps are considered the basis ECG data. All records in this data set have non-missing QTcF change from baseline (ΔQTcF) and non-missing ECG date and time.

5.5.2 PK concentration data

The basis PK concentration data for PK-ECG matching will include all concentrations that are not missing and have non-missing sample date and time.

5.5.3 Algorithm to match PK and ECG data

One-to-one matching using the basis ECG data and basis PK concentration data is defined as the PK/ECG data. Such dataset is used in the PK-QTc analysis and is established based on the following algorithm:

To be considered for a match, the ECG date/time should be within 15 minutes of PK sample date/time, inclusive; the closest record (that is not already matched with PK) should be chosen if there are multiple matched ECG measurements; the ECG record after the PK sample/date time should be chosen if there are more than one closest match.

6 Reference

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.

Novartis internal criteria for Common Toxicity Criteria (CTC) grading of laboratory parameters


CTC grading 4.03.pdf

ICH guideline E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (R3) - questions and answers


ICH_E14_qtc-interval-prolongation.pdf