NOVARTIS

Clinical Development

PDR001 and LAG525

CPDR001XUS01 / NCT03365791

Modular phase 2 study to link combination immune-therapy to patients with advanced solid and hematologic malignancies
Module 9: PDR001 plus LAG525 for patients with advanced solid and hematologic malignancies

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
05-July-19	*Pre-DBL*	*In order to write abbreviated CSR, team has decided to exclude some summary tables from the analysis*	*Remove Screen failure reason, Prior- Antineoplastic therapy and Antineoplastic therapy since discontinaution of study drug summary tables detail from the relavant sections*	*Section 2.3.1 Patient disposition and section 2.4.2 Prior and , concomitant and post therapies*
08-Nov-20		During dry run some table's layout is modified/updated. As per team's confirmation mockshells are being updated	Remove outputs Summary of AE findings, AE due to infusion reaction by SOC and PT, Number of treatment cycles added.	Section 2.2.3, 2.3.1, 2.81 modified.
29-Jan-21	*Post-DBL*	*Few changes were made to provide more clarity and accuracy in the reports*	*Protocol deviation was summarized using Full analysis set population, however it was observed that one patients was being excluded from the report hence the population was updated to All patients.* *Listing 14.3-2.1 Title was mentioned as "Deaths during treatment", however it was decided that Title need to be update as "Deaths during study" and to know which deaths occurred during treatment one extra column was added as "Observation/Period". The footnote was also updated for the same in the listing as below* *"- 1-Pre-treatment period: from day of patient's informed consent to the day before first administration of study drug ,-2-On-treatment period: from day of first administration of study drug to 30 days after last administration*	*Protocol deviation Table and listing.* *Listing 14.3-2.1*

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			of study drug,- 3-Extended safety follow-up period: from day 31 to at least day 150 after last administration of study drug or lost to follow-up"	
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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes detailed statistical methodology for the analysis of data from study CPDR001XUS01. Study treatment under evaluation in this study are PDR001 and LAG525.

The primary efficacy variable, clinical benefit rate, will be analyzed by a Novartis designated Contract Research Organization (CRO), [redacted]. Analysis details are provided in Appendix 4 of the protocol, which is also included in Section 2.5 of this Statistical Analysis Plan.

All other data will be analyzed by Novartis or designated CRO, according to Section 10 of the study protocol which will be available in Appendix 16.1.1 of the Clinical Study Report(CSR). Important information is given in the following sections and details will be provided, as applicable, in Appendix 16.1.9 of the CSR. All statistical analyses will be performed using SAS® Version 9.4 (or higher).

1.1 Study design

1.1.1 Description of study design

This is a phase II, open-label study to determine the efficacy and safety of treatment with the combination of PDR001+LAG525 across multiple tumor types that are relapsed and/or refractory to available standard of care therapies. The study will be conducted in 35-210 patients with select solid tumors or lymphoma as outlined in Table 1-1 Tumor GroupsSeven pre-specified tumor cohort (groups) planned for the analysis are as follows:

Table 1-1 Tumor Groups

Group	Malignancy
1	Small-cell lung cancer
2	Gastric/esophageal adenocarcinoma
3	Castration resistant prostate adenocarcinoma (CRPC)
4	Soft tissue sarcoma
5	Ovarian adenocarcinoma
6	Advanced well-differentiated neuroendocrine tumors
7	Diffuse large B cell lymphoma (DLBCL)

Tumor cohorts may be excluded or added during the course of the study in the case of early futility or success based upon an interim analysis or at the discretion of Novartis based on emerging pre-clinical or clinical data .

Patients will receive study treatment for a maximum of 2 years, or until disease progression, unacceptable toxicity, death or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, start of a new anti-neoplastic therapy or at the discretion of the investigator or patient). 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.

1.1.2 Enrollment model

This study is intended for patients who have a pathologically confirmed diagnosis of any tumor listed in Table 1-1, and have relapsed and/or refractory disease. Once the patient has been identified, treating physicians who are qualified investigators may contact Novartis or designee to consider enrollment in the appropriate tumor cohort. Informed consent must be signed before any screening activities take place. If all eligibility criteria are met (see Section 5 of protocol), the patient will initiate therapy with the combination of PDR001 and LAG525. The patient may not receive any additional anti-cancer therapy during treatment with PDR001 and LAG525.

1.1.3 Tumor group enrollment schema

Accrual to each tumor group will consist of a futility and expansion stage based on the observed 24 week CBR rates. The 24 week CBR rate will be continually assessed for futility and early success by comparing posterior quantities for the rate to pre-specified futility and expansion criteria for each group(see Section 10 of protocol). Analysis for both futility and expansion will borrow information across cohorts with a hierarchical model (see Section 10 of protocol). The hierarchical model allows dynamic borrowing of information between groups such that more borrowing occurs when the groups are consistent and less borrowing occurs when the groups differ. In this way, the model is a compromise between the two alternate extremes of either a completely pooled analysis or a separate analysis in each group.

Depending on whether or not pre-specified criteria for stopping (for futility) or continuing enrollment (for early success) is met, each tumor group can enroll a minimum of 5 patients and a maximum of 30 patients during the course of the study. When at least 5 patients within a group have completed 24 weeks of treatment and have CBR data available, analysis for futility and early success (expansion) will commence to inform a “go/no-go" decision for that group. For tumor groups in which treatment is not declared futile and pre-specified CBR rate for early success is met, a “go” decision will be made to continue enrolling to a maximum of 30 patients for that group.

Expanded tumor groups will continue to have ongoing analysis for futility to allow for early stopping in the event that observed 24 weeks CBR rates do not meet prespecified final success criteria (see Section 10 of protocol). For tumor groups in which treatment has not been declared futile, but criteria for expansion has not been met, enrollment will be paused at 10 patients until a “go/no-go” decision can be made based on information gleaned from the dynamic borrowing of CBR data across tumor groups (see Section 10 of protocol).

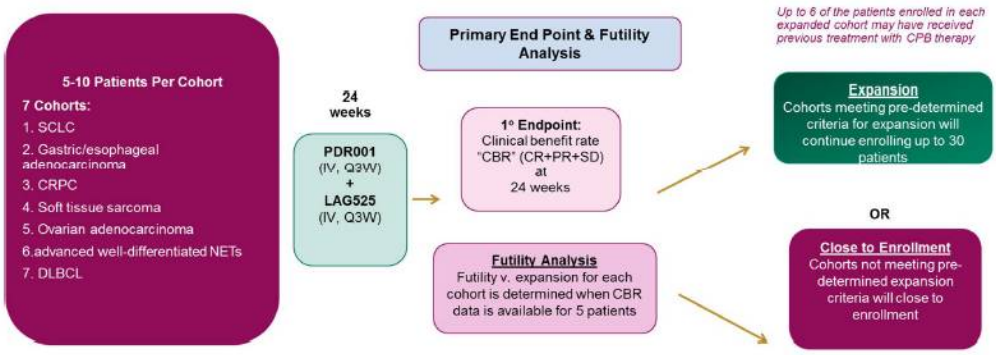
A “no-go” decision can be made for a tumor group if: 1) 24 week CBR rates of the first 5-10 patients show treatment to be futile and group will not expand; 2) subsequent analysis in a group

that expanded fails to demonstrate continued evidence of activity such that 24 weeks CBR is not predicted to meet pre-specified criteria for final success (See Section 10 of protocol).

Those patients who discontinue study treatment for any reason other than disease progression or treatment related toxicity may be replaced (at the discretion of Novartis), until at least 5 patients with 24 weeks of CBR data are accrued within a cohort. All patients enrolled into a tumor group prior to expansion must not have been exposed to prior immuno-oncology (IO) therapy. Once a tumor group is selected for expansion, the group shall continue to enroll patients until the group enrolls a total of 30 patients.

A schematic representation of the study design is shown in Figure 1-1.

Figure 1-1 Study design



1.1.4 Early study termination

The study can be terminated at any time for any reason by Novartis.The patient should be seen as soon as possible for End of Treatment (EOT) visit and the same assessments for EOT should be performed as described for a discontinued or withdrawn patient.

1.1.5 End of study

Patient accrual to the study will end when all tumor groups have completed initial futility and expansion analysis and all expanded groups have accrued 30 patients. The study will end when all enrolled patients have either discontinued or completed 2 years of study therapy and 150 days of safety follow up.

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-2 below.

For patients with solid tumors the assessment criteria will be RECIST 1.1

For patients with lymphoma, the assessment will be based on Revised Response Criteria for Malignant Lymphoma (Cheson et al 2007).

Table 1-2 Objective and related endpoints

Objective	Endpoints
Primary	
• To assess clinical benefit rate (CBR) at 24 weeks of PDR001+LAG525 by tumor type in multiple solid malignancies and lymphoma.	• The primary endpoint is CBR after 24 weeks of treatment with PDR001+LAG525 based on local investigator assessment.
Secondary	
• To assess overall response rate (ORR) in solid tumors and in lymphoma. • To assess Time to response (TTR), Duration of response (DOR), Time to progression (TTP) and Progression free survival (PFS) rate at 1 and 2 years • To assess Safety and Tolerability	• Endpoint is ORR evaluated based on the PR and CR, based on local investigator assessment. • Endpoints are TTR, DOR, TTP and PFS rate at 1 and 2 years • Safety incidence and severity of adverse events (AEs) and serious adverse events (SAEs) including changes in laboratory parameters, vital signs and ECG. Tolerability: Dose interruptions, reductions and dose intensity

2 Statistical methods

2.1 Data analysis general information

Data from all centers that participate in this protocol will be used. Data used for the analyses specified in this document will come from the Electronic Data Capture (EDC) system.The analyses stated in this document will be based on all patients' data up to the time when all enrolled patients have either discontinued or completed 2 years of study therapy and 150 days of safety follow up.

All statistical analyses presented in this document are related to patient background information, efficacy, and safety. All analyses are descriptive and no hypothesis testing is planned (except for the primary efficacy variable, which is described in Section 2.5 below). For continuous data, the number of observations, mean, standard deviation (SD), median, 25th and 75th percentiles,

minimum, and maximum will be presented. For categorical data, frequencies and percentages will be presented.

In general, data from all centers will be combined for any analysis. There will be no stratification factor considered for the analysis with the exception of tumor type in the primary efficacy variable analyses. Missing data will not be imputed. All data collected in the study will be presented in the listings.

2.1.1 General definitions

2.1.1.1 Study drug and study treatment

- For this study, the terms "investigational or study drug" refers to 'PDR001' or 'LAG525'.
- "Study treatment" refers to investigational drug PDR001 + investigational drug LAG525.

2.1.1.2 Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a non-zero dose of study drug was administered and recorded on the Dose administration record (DAR) CRF. For the sake of simplicity, the date of first administration of study drug will also be referred as start date of study drug.

2.1.1.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on the DAR CRF.

2.1.1.4 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered and recorded on the DAR CRF. For example, if the 1st dose of study drug A is administered on 04JAN2016, and the 1st dose of its combination partner, drug B, is administered on 03JAN2016, the date of the first administration of study treatment is on 03JAN2016. For the sake of simplicity, the date of the first administration of study treatment will also be referred as the start date of study treatment.

2.1.1.5 Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered and recorded on the DAR CRF. For example, if the last dose of study drug A is administered on 15APR2016, and the last dose of a combination partner, drug B is administered on 17MAY2016, the date of last administration of study treatment is then on 17MAY2016.

2.1.1.6 Study day

The study day for all assessments (both efficacy and safety) will be calculated as the difference between the date of the event (visit date, onset date of an event, assessment date, etc.) and the start date of study treatment plus one day. The first day of study treatment is therefore study day 1. The study day for all pre-treatment assessments will be calculated as the difference between the date of the event and the start of study treatment. The last day prior to study treatment intake is therefore Study Day -1.

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

2.1.1.7 Baseline

Baseline (e.g. for laboratory parameters), is considered as the last available assessment or value before start of the first treatment, unless otherwise stated under the related assessment. For all relevant parameters comparisons against baseline will be presented through the report.

Baseline could be within 21 days before first treatment administration or on the same day as first treatment administration if specified pre-dose. Specific assessments may be performed more than 21 days prior to day 1 of dosing. Such cases will also be considered as baseline, if no other assessments are performed thereafter, prior to day 1 of dosing. Patients with no data on a particular parameter before the first treatment administration will be considered to have a missing baseline for this parameter.

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

General guidance for baseline definition:

Dependent on the variable, the baseline assessment will be done at screening (Day -21 to 1) or baseline (Cycle 1 Day 1 [C1D1]). Baseline assessments should be obtained before the first study treatment intake based on the variables. Any assessment which is obtained outside of the protocol-defined screening period will not be considered for baseline unless otherwise specified.

2.1.1.8 On-treatment assessment/event and observation periods

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

1. Pre-treatment period: from day of patient's informed consent to the day before first administration of study drug

2. On-treatment period: from day of first administration of study drug to 30 days after last administration of study drug (Note: for ongoing patients, from day of first administration of study drug to the analysis cut-off date)

3. Extended safety follow-up period: from day 31 to at least day 150 after last administration

of study drug or lost to follow-up.

In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period, the so-called treatment-emergent AEs.

All safety data (including those from the pre-treatment and extended safety follow-up period) will be listed and those collected during the pre-treatment and extended safety follow-up period are to be flagged.

Additional summaries will be displayed to report deaths, all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after last administration of study drug.

2.1.1.9 Year, month and week

For reporting purpose below mentioned rule will be followed to convert a year, month and week in days.

1 year = 365.25 days

1 month = 30.3475 days

1 week = 7 days

2.2 Analysis sets

2.2.1 Full analysis set

The Full Analysis Set (FAS) will include all patients who have received at least one dose of study treatment. FAS will be used for the analysis of efficacy endpoints.

If a patient does not have any post-baseline assessment that patients will not be included in FAS.

2.2.2 Safety set

The Safety Set will include all patients who received at least one dose of study treatment.

2.2.3 Subgroup of interest

Some specific efficacy analyses will also be repeated in the following subgroup as appropriate. .

1. Tumor cohorts.
2. Prior line of therapy(1,2,and >=3)
3. Number of treatment cycles(less than 3 cycles,>= 3cycles, Less than 5, >=5 cycles)

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.

2.3.1 Patient disposition

The following summaries will be provided: % based on the total number of FAS patients:

Treatment phase:

- Number (%) of patients who are still on-treatment (based on the [End of Treatment Phase Disposition] eCRF page not completed);
- Number (%) of patients who have discontinued the study treatment phase (based on the [End of Treatment Phase Disposition] eCRF page);
- Primary reason for study treatment phase discontinuation (based on the [End of Treatment Phase Disposition] eCRF page
- Number (%) of patients who have entered the post-treatment safety follow-up (based on the [End of Treatment Phase Disposition] eCRF page);
- Number (%) of patients who are still in the post-treatment safety follow-up phase (based on the [End of Post Treatment Phase Disposition] eCRF page not completed);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'End of Post Treatment Follow-up Disposition' page).
- Reasons for discontinuation from the post-treatment follow-up (based on 'End of Post Treatment Follow-up Disposition' page).

The patient disposition data will be listed for the FAS. All screen failure patients (i.e., patients who discontinued during screening phase) will also be listed along with the relevant information such as reason(s) for screening phase discontinuation.

Protocol deviations

The number (%) of patients with any CSR-reportable protocol deviations (PDs) will be tabulated based on All patients.All protocol deviations will be listed. All PDs will be reviewed during the study and finalized before clinical database lock. All patients will be used to summarize the data.

Analysis sets

The number (%) of patients in each analysis set (defined in Section2.2) will be summarized and listed .

Patient background, demographics and baseline characteristics

Demographic and baseline characteristics data, disease characteristics, medical history, and prior anti-neoplastic therapies are collected at the screening visit. Descriptive summaries and/or listings will be provided. The FAS analysis set will be used for the summarizing the data. .

Demographic and baseline characteristics

Demographic characteristic variables include:

- Age (years)
- Age category
  - <65 years
  - ≥65 years
  - missing
- Sex
  - Male
  - Female
  - missing
- Race
  - Caucasian
  - Black
  - Asian
  - Native American
  - Pacific Islander
  - Other
  - missing
- Ethnicity
  - Hispanic/latino
  - Chinese
  - Indian
  - Japanese
  - Other east Asian
  - Southeast Asian
  - West Asian
  - Mixed ethnicity
  - Other
  - missing
- Child bearing potential for female patients
  - Able to bear children
  - Premenarche
  - Post menopausal
  - Sterile-of child bearing age

Baseline characteristic variables include:

- Eastern Cooperative Oncology Group - Performance Status (ECOG PS)
  - 0 - Fully active, able to carry on all pre-disease performance without restriction
  - 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
  - 2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

  - 3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
  - 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
  - Missing
- Body weight (kg)
- Body height (cm)
- Body surface area (BSA) (m^2)
  BSA to be calculated as per the DuBois and DuBois formula:
  = 0.20247 x height(m)^0.725 x weight(kg)^0.425
- Cardiac imaging (Left Ventricular Ejection Fraction [LVEF])
- Body mass index(BMI)(kg/m^2)
  BMI to be calculated as (weight[kg] / (height[m]2) using weight at baseline.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: diagnosis of disease, details of tumor histology/cytology (based on predominant histology/cytology), histological grade, stage at initial diagnosis, time since initial diagnosis to first administration of study drug (in months), time since most recent relapse/progression to first administration of study drug (in months), stage at time of study entry, types of lesions at baseline, and number and type of metastatic sites involved.

Note: Types of lesions at baseline (presence/absence of target and non-target lesions and index and non-index lesions) will be based on the data collected on the [RECIST 1.1 Target Lesion Assessments], [RECIST 1.1 Non-Target Lesion Assessments],[Cheson tumor evaluation - Index lesion] and Cheson tumor evaluation – Non-Index lesion] eCRF pages. Metastatic sites will be based on the [Diagnosis and Extent of Cancer] eCRF page.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

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

The safety set will be used for all analyses associated with study treatment and other medications/non-drug therapy.

2.4.1 Study treatment

The duration of exposure (weeks), cumulative dose, actual dose intensity and relative dose intensity will be listed and summarized for the study drugs PDR001 and LAG525 based on safety set by means of descriptive statistics. Categories for relative dose intensity of PDR001 and LAG525 will be specified as ≤ 75%, >75% - ≤90%, > 90% - ≤ 110% and > 110%; the number and proportion of patients within each category will be presented.

In addition, dose interruptions and dose permanently discontinued (including the reasons for these) will be listed and summarized. All dosage administration records will be listed.

Duration of exposure to study treatment

Duration of exposure to study treatment is calculated as follows:

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

Duration of exposure (weeks) = (Duration of exposure, days) / 7.

The last date of exposure to PDR001 Q3W is the planned end date of the last cycle in which the last non-zero dose of PDR001 was last administered (i.e last date of administration + 20 day)).

Similarly, the last date of exposure to LAG525 Q3W is defined as the last date of LAG525 administration + 20 days.

The last date of exposure for the combination PDR001+LAG525 is the last date of exposure to PDR001 or LAG525 (defined as above), whichever is later.

Note: If the patient died or was lost to follow-up before the derived last date, the last date of exposure to investigational drug/study treatment is the date of death or the date of last contact, respectively.

Summary of duration of exposure of study drug in appropriate time units will include categorical summaries (<6, 6-<12, 12-<18, 18-<24 and ≥24weeks) and continuous summaries (i.e. mean, standard deviation etc) in weeks. The duration of exposure to study drug may include periods of temporary interruption (zerodose periods).

Actual cumulative dose

Actual cumulative dose is defined as the total dose administered over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF,and will be summarized for each of the study treatment components separately.

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

- Actual dose (mg) = Sum of (actual dose per an infusion) for all infusions.

Dose intensity and relative dose intensity

The dose intensity(DI), expressed as mg/*unit of time*, and the relative dose intensity(RDI) are defined as follows:

- Dose intensity (mg/ *unit of time*) = (Actual cumulative dose, mg) / (Duration of exposure, *unit of time*).

- Relative dose intensity(%) = (Dose intensity, mg/*unit of time*) / (Planned dose intensity, mg/*unit of time*)*100.

Planned dose intensity (mg/*unit of time*) can be calculated as follows:

- Planned dose intensity (mg/unit of time) = (Planned cumulative dose, mg) / (Duration of exposure,*unit of time*)

- Planned cumulative dose (mg) = Sum of (dose prescribed, mg) for all infusions

Dose interruptions and permanent discontinuations

The number of subjects who have dose interruptions, permanent discontinuations, and the reasons, will be summarized separately for each of the study treatment components.
'Dose permanently discontinued' from the Dosage Administration CRF pages (DAR) will be used to determine the permanent discontinuations, and Dose interruption is defined as any dose interruption flagged in the Dosage Administration CRF pages (DAR), satisfying the following criteria:

- a reason other than 'As per protocol',
- occurs between the first and last non-zero doses,
- follows a non-zero actual dose.

The corresponding fields 'Reason for dose interrupted', 'Reason for permanent discontinuation' will be used to summarize the reasons. Dose reductions are not permitted for PDR001 and LAG525.

Additionally, treatment beyond RECIST progression will be summarized based on safety set.

2.4.2 Prior concomitant and post therapies

Prior anti-neoplastic therapies

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized overall.

This summary will include medication: type of last therapy,setting at last therapy and best response to last medication. A separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

The above analyses will be performed using the FAS. Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA.

Post treatment anti-neoplastic therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed for the FAS in three separate listings: medications, radiotherapy, and surgery.

Concomitant therapy

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include 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 World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. Concomitant medications with immunosuppressive intent will be summarized by lowest ATC class and preferred term using frequency counts and percentages. Concomitant medications with immunosuppressive intent will be summarized by lowest ATC class and preferred term using frequency counts and percentages. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and

2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Additional summaries will be provided to report medications starting between 31 days after last dose of study PDR001 and 150 days after last dose of PDR001. All reported concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of PDR001 or starting more than 150 days after the last dose of PDR001 will be flagged in the listing. The safety set will be used for all concomitant medication tables and listing.

2.5 Analysis of the primary objective

The primary objective is to assess the clinical benefit of treatment with PDR001 + LAG525 at 24 weeks of treatment based on local investigator assessment.

2.5.1 Primary endpoint

The primary endpoint is the clinical benefit rate (CBR) (e.g. defined as CR, PR or SD) at week 24 by RECIST 1.1 for solid tumors and the Revised Response Criteria for Malignant Lymphoma, (Cheson et al 2007), for Lymphoma.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy variable CBR is as defined below.

CBR at 24 weeks:. CBR is defined as the proportion of patients with a best overall response of CR or PR or SD within the first 24 weeks of treatment.

In addition to tumor-specific measurements (e.g., radiological assessment of tumor response for solid tumors), progressive disease will also be considered when it was indicated either as a reason for the study treatment discontinuation or as a cause of on-treatment death. CR and PR (for solid tumors) require a confirmation that is at least a minimum of 4 weeks after the initial observation of response. Patients who had confirmed CR/PR or SD prior to or at 24 weeks, will be considered as achieving clinical benefit; patients who had confirmed CR/PR/SD prior to or at 24 weeks, but progressed at or after 24 weeks will also be considered as achieving clinical benefit.
CBR will be analyzed by comparing achieved CBR with a historical control rate of each tumor type, and if there is at least 80% probability that the response rate in a tumor type exceeds the historical rate, then the tumor type will be considered a success.

CBR will be analyzed, as mentioned below, by a Novartis designated vendor, [redacted].

The study will enroll patients from 7 tumor cohorts as mentioned in Section 1.1 study design.

We let Y_i be the response indicator for the i^{th} subject, and let R_g be the assumed probability of response within a control population and $\pi_g = \Pr(Y_i = 1 \mid g_i = g)$ be the underlying probability of response for group g within the trial. We transform to the logit scale for modeling purposes. Let θ_g be the mean log odds treatment effect, i.e.:

$$\theta_g = \log\left(\frac{\pi_g}{1-\pi_g}\right) - \log\left(\frac{R_g}{1-R_g}\right)$$

Thus, θ_g is the group specific logistic regression coefficient for group g. The primary analysis is a set of group specific tests that $\theta_g>0$, meaning that the treatment is better than the assumed control rate for that group. Thus, we wish to test the set of hypotheses

$$H_{0g} : \theta_g \leq 0$$

$$H_{1g} : \theta_g > 0$$

We proceed in a Bayesian fashion, assigning a prior distribution (discussed below) and computing the posterior probability of H_{1g} within each group g. If, at the final analysis,

$$\Pr(\theta_g > 0 \mid \text{data}) > 0.80$$

then group g will be declared a success. Hence, the final analysis produces a separate decision for each group. The trial allows for early stopping of groups for futility, described below. No early stopping for success is allowed.

The statistical design borrows information across subgroups with a hierarchical model. The hierarchical model allows dynamic borrowing of information between groups such that more borrowing occurs when the groups are consistent and less borrowing occurs when the groups differ. In this way, the model is a compromise between the extremes of a completely pooled analysis as opposed to a separate analysis in each group. We additionally incorporate a clustering mechanism that allows borrowing within clusters but treats clusters separately. This minimizes borrowing across groups that are quite different in terms of CBR effects.

The hierarchical model approach involves two stages. The goal of both stages is to allow the data to drive the amount of borrowing across groups. If the data indicate a large amount of borrowing is appropriate (due to similar results), the model will borrow more and thus increase the overall power of the trial within each group. In contrast, if the data indicate a small amount of borrowing is appropriate (due to dissimilar results) the model will adjust and each group will stand more on its own. This "dynamic" borrowing property is distinct from other approaches which use a fixed informative prior or apriori assume an amount of borrowing across groups. Here the approach includes two stages to identify the appropriate amount of borrowing based on the data.

The first stage of model places the groups into distinct clusters. The purpose of this stage is to minimize borrowing of information across groups that appear to be quite different. Thus, for example, should 2 of the groups appear similar while the others differ significantly, the model may place a large probability on two clusters, one containing the two similar groups with the other containing the remaining groups. The model does not pick one particular clustering, but instead incorporates the uncertainty of the data in this determination, producing a probability distribution over the possible clustering. Thus, in our example, the model may consider it highly likely that the 2 similar groups are in one cluster with the remaining groups in another, but it would also retain lower probabilities on the possibility all groups are in one cluster (e.g. we are simply seeing differences in the two groups by chance) as well as other possibilities. The complete analysis averages over this uncertainty.

At the second stage, we place hierarchical models over the groups within each cluster (thus, conditional on the clustering, there is no borrowing of information across clusters, only within clusters). The hierarchical model assumes that the θ_g have an across groups distribution

$$\theta_g \sim N(\mu, \tau^2)$$

The across group mean μ and variance τ^2 are unknown, and hence have a prior distribution which is combined with the data to produce estimates of μ and τ^2.

The variance component τ controls the degree of borrowing among groups. Small values of τ result in a greater degree of borrowing while large values of τ correspond to less borrowing. The parameter τ is estimated using the data, so the observed between group variation is a key component of the model behavior.

Combined, the two stages allow groups with similar results to borrow information between them (they will have a high probability of being in the same cluster) while groups with different

results with borrow far less information between them (they will have a low probability of being in the same cluster).

Details of the hierarchical model is provided in Appendix 4 of protocol.

Evaluation of trial success and futility

Interim monitoring will occur once 5 subjects have CBR data available within a cohort. Interim analyses will continue every 3 months thereafter provided at least 10 subjects contribute new CBR data to the subsequent interim. Simulation studies in this document approximate this interim plan, as they are timed 12 weeks apart without any restrictions on the number of new observations within the analysis.

At each interim analysis, the groups will be evaluated for early futility and sample size expansion by comparing posterior quantities for the CBR to pre-specified early stopping criteria.

Table 2-1 Historical CBR for each group

Group Index	Tumor Type	Median PFS (mo.)	Hist. CBR (%)	Hypothetical Yearly Average Accrual (Subjects)
1	SCLC	1.5	6.25	20
2	Gastroesophageal	5	43.50	16
3	STS	6.2	51.10	13
4	Prostate	4	35.40	11
5	Ovarian	3	25.00	10
6	Advanced NET	5	43.50	7
7	DLBCL	3	25.00	6

Early Futility

If there is less than 20% probability that the response rate in a subgroup exceeds the historical rate R_g, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$\Pr(\pi_g > R_g) < 0.20.$$

A group is only eligible for early stopping once a minimum of 5 patients have been evaluated for response in that group.

Early Success

If there is at least 70% probability that the response rate in a subgroup exceeds the historical rate, then the subgroup will stop enrollment early for success. Formally, enrollment will stop early for success if:

$$\Pr(\pi_g > R_g) > 0.70.$$

A minimum of 5 subjects will need to be evaluated prior to declaring a group to be efficacious. This eligibility remains effective until the next interim analysis is conducted, at which point eligibility is re-evaluated based on the currently available data and corresponding model outcomes.

Post-Expansion Futility

If there is less than a 60% probability that the clinical benefit rate in a group exceeds the historical rate, then the group will stop enrollment early for futility. Formally, enrollment will stop early for futility if:

$$\Pr(\pi g > Rg) < 0.60.$$

A group is only eligible for this post-expansion stopping criterion once the group has expanded to a sample size beyond 10 subjects enrolled. Note this post-expansion futility is a stricter futility rule than that used prior to sample size expansion.

Final Analysis

The final analysis will occur when both accrual and follow-up are complete for all groups. If, at the completion of the trial, there is at least 80% probability that the response rate in a group exceeds the historical rate, then the group will be considered a success. Formally:

$$\Pr(\pi_g > R_g) > 0.80.$$

In addition of above mentioned Bayesian analyses with all solid tumor types combined and separately for each hematological tumor type, the CBR estimate will be provided with its 95% exact CI. For tumor types (within the solid tumors) that have ten (10) or more patients, separate summaries will be performed by the tumor type and will also be displayed graphically. In the event that there are fewer than 4 patients for a hematological tumor type, only listing will be provided for that tumor type. In addition to summary by tumor types, separate summaries will also be provided by prior line of therapy and number of treatement cycles received.

CBR estimate with its 95% exact CI will also be provided for CBR by end of study using full analysis set. Additionally, for tumor cohort Prostate cancer an association of response(CBR) with PSA(prostate specific antigen) will be explored by summarizing the response at different level of PSA stratified by quartiles at baseline and 24 week.Similar analysis will also be repeated for ovarian cancer with Cancer Antigen-125 (CA-125).

2.5.3 Handling of missing values/censoring/discontinuations

For the computation of CBR (CR, PR or SD) in case of solid tumor all confirmed responses (CR or PR) reported up to the analysis cut-off will be included. Patients with no valid radiological assessment or unconfirmed responses will be considered as non-responders. In particular, patients with CR or PR at the last radiological assessment prior to cut-off and no response at the previous assessment are by definition unconfirmed and will be considered as non-responders for the primary analysis.

Patients with unknown or missing BOR will be counted as failures (non-responders). If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be ‘Unknown’. If no valid post-baseline tumor assessments are available, the BOR must be

'Unknown' unless progression is reported. For the computation of CBR, these patients will be included in the FAS and will be counted as 'non-responders'.

2.5.4 Supportive analyses

Not Applicable.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

Not Applicable

2.6.2 Statistical hypothesis, model, and method of analysis

Not Applicable

2.6.3 Handling of missing values/censoring/discontinuations

Not Applicable

2.7 Analysis of secondary objective(s)

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

The secondary objectives for this study are as follows:

- To assess overall response rate (ORR) by RECIST 1.1 in solid tumors and by Revised Response Criteria for Malignant Lymphoma (Cheson et al 2007) in lymphoma
- To assess TTR, DOR, TTP and PFS rate at 1 and 2 years
- To assess safety and tolerability of the study drugs

2.7.1 Secondary endpoints

The secondary endpoints of this study are as follows:

- Overall response rate (ORR): ORR is determined by investigator assessment for each tumor assessment in the study. For patients with solid tumors, the assessment criteria will be RECIST 1.1 and will include responses of CR and/or PR for ≤24 weeks. For hematological tumors, other appropriate criteria (see Protocol Appendix section for corresponding criteria) will be used to determine the responses. Additionally,estimates with corresponding 95%CI will also be provided for ORR by end of study.
- Time to Response(TTR) defined as the time from the date of first dose to the date of first documented response of CR or PR. All patients will be included in time to response calculation. For solid tumor patients who did not achieve a confirmed PR or CR will be censored
    - at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause)
    - at last adequate tumor assessment date otherwise.

- Time to Progression (TTP) defined as the time from the date of first dose to the date of first documented disease progression or relapse. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment. Died subjects without documented progression will also be censored at the at the date of last adequate tumor assessment

- Duration of Response (DOR) defined as the time from the first documented response to the date first documented disease progression or relapse or death due to any cause. DOR applies only to patients who responded, e.g., for solid tumor, responder is defined as the patient's best overall response being CR or PR. The start date is the date of first documented response, and the end date is the date of event defined as the first documented progression/relapse or death due to any cause within 150 days of the last study drug dose date. In other words, the start date will be determined using the time the response was first determined and not using the time the response was confirmed. If a patient has not had an event, duration is censored at the date of last adequate tumor assessment.
- Progression Free Survival (PFS) defined as the time from the date of first dose to the date of first documented disease progression or relapse or death due to any cause during study medication or within 150 days from last dosing date, and is calculated as PFS = (date of progression/relapse or death – date ofirst study treatment + 1). Disease progression noted as the reason for discontinuation of treatment will also be considered as a progression event for PFS analyses. If a patient has not had an event, progression free survival is censored at the date of last adequate tumor assessment
- Safety and tolerability based on number of incidences of AEs, SAEs, severe AEs, changes in laboratory parameters, vital signs and ECGs, drug interruption, reduction and dose intensity.

2.7.2 Statistical hypothesis, model, and method of analysis

The overall response rate (ORR, PR plus CR) and its two sided exact binomial 95% confidence interval will be provided for each patient group. The number and percentage of patients for different categories of overall response (e.g., for solid tumor - CR, PR, SD, PD, and NE) will be presented. These analyses will be performed with all solid tumor types combined and separately for each hematological tumor type. For tumor types that have ten (10) or more patients (within the solid tumors), separate summaries will be performed by the tumor type. In the event that there are fewer than 4 patients for a hematological tumor type, only listing will be provided for that tumor type. Additionally, the above analysis will also be repeated for overall response rate by 12 weeks and 18 weeks.
Components of tumor assessments (target lesion response, non-target lesion response, new lesion [yes/no]) will be listed. In addition, Cancer Antigen-125 (CA-125) in the assessment of ovarian cancer response, or Prostate-specific antigen (PSA) in the assessment of prostate cancer response will also be listed.

PFS, TTP and TTR will be summarized and graphed using the Kaplan-Meier product-limit method for each patient group. The estimates of the 25th, median, 75th percentiles of the PFS and their 95% confidence intervals will be provided, if applicable. Analyses will be based on

all tumor types combined. For tumor types, separate summaries will be performed by the tumor type.
DOR will be summarized using the Kaplan-Meier method and the median response presented along with 95% confidence interval only if there are sufficient numbers of events, otherwise, only listing of DOR will be provided. Analyses will be based all tumor types combined.

Additionally, a swimmer plot depicting time to onset and duration of response per RECIST 1.1 based on local radiology review will be presented.
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2.7.3 Handling of missing values/censoring/discontinuations

Handling of missing tumor assessments in ORR analysis

For the computation of ORR, in case of solid tumor all confirmed responses (CR or PR) reported up to the analysis cut-off will be included. Patients with no valid radiological assessment or unconfirmed responses will be considered as non-responders. In particular, patients with CR or PR at the last radiological assessment prior to cut-off and no response at the previous assessment are by definition unconfirmed and will be considered as non-responders for the primary analysis.

Patients with unknown or missing BOR will be counted as failures (non-responders). If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the BOR must be 'Unknown' unless progression is reported. For the computation of ORR, these patients will be included in the FAS and will be counted as 'failures'.

Censoring rules TTP and PFS calculation

If a patient has not progressed or is not known to have died due to underlying cancer or has received any further anti-neoplastic therapy in the absence of progression, at the analysis cutoff date, will be censored at the date of the last adequate tumor assessment before the cut-off date or before the start of the new anti-neoplastic therapy date, whichever is earlier. Patients who do not have any post-baseline tumor assessment will be considered as censored at Day 1.

2.8 Safety analyses

All safety analyses will be based on the safety set, and follow the definitions of on-treatment assessment/event and observation periods specified in Section 2.1.1, unless otherwise specified.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period (Section 2.1.1). All AEs collected in the [Adverse Events] eCRF page will be listed along with the information collected on those AEs, e.g., AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings. All deaths collected in the [Death] eCRF page will be listed along with the reason.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT)

using MedDRA coding. A 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 preferred term will be summarized under the maximum CTCAE grade recorded for the event.

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

The following AE summaries will be produced by SOC and PT (and maximum grade, as needed);

- AEs, regardless of study drug relationship
- AEs, suspected to be study drug related
- Adverse events, regardless of study drug relationship, by preferred term
- Most frequent adverse events, regardless of study drug relationship, by preferred term (> x%)
- SAEs, regardless of study drug relationship
- SAEs, suspected to be study drug related
- AEs leading to study drug discontinuation, regardless of study drug relationship
- AEs requiring dose adjustment or interruption, regardless of study drug relationship

In addition, overall summary of AEs (including deaths) will be produced. Separate listing will be produced for SAEs.

AEs during on-treatment or extended safety follow-up period

AE monitoring should be continued for at least 150 days following the last administration of study drug. In addition to the treatment-emergent (on-treatment) AE summaries described above, the supportive summaries of all AEs,treatment-related AEs occurring during the on-treatment period or extended follow-up period will be produced in a similar manner.

The following AE summaries will be produced by SOC and PT (and maximum grade, as needed) for all AEs occurring during the on-treatment period or extended follow-up period;

- AEs, regardless of study drug relationship
- AEs, suspected to be study drug related
- SAEs, regardless of study drug relationship
- SAEs, suspected to be study drug related

2.8.1.1 Adverse events of special interest / grouping of AEs

Not Applicable

2.8.2 Deaths

The number and percentage of patients who died within 30 days of the last dose will be and all deaths (during the on-treatment and extended safety follow-up period) summarized with cause of deaths. Additional summary will be displayed to report all deaths up to 150 days

after last administration of study drug.

If study indication is primary reason for death (and not coded accordingly in the database) it must be included in the summary table. A patient listing of all deaths with recorded principal cause of death (if available) will also be provided, deaths during the extended safety follow-up period will be flagged.

2.8.3 Laboratory data

All laboratory values will be converted into SI units and the severity grade will be calculated using appropriate common terminology criteria (CTCAE v4.03).

A severity grade of 0 will be assigned when the value is within normal limits. For lab parameters for which severity grades are determined both through normal limits and absolute cut-offs, in the unlikely case when a local laboratory normal range overlaps into the higher (i.e. non-zero) CTCAE grade, the laboratory value will still be taken as within normal limits and assigned a CTCAE grade of zero.

The results will be listed separately for hematology and biochemistry laboratory tests, along with details on the CTCAE grades and/or classifications relative to laboratory normal ranges.

The results will be summarized separately for hematology and biochemistry laboratory tests as mentioned below:

1. Shift table from baseline to worst value on-treatment value, for those lab tests having CTCAE grades (frequency count and percentages)
2. Shift table from baseline to worst on-treatment value, for those lab tests not having CTCAE grades, based on the low/normal/high classification (frequency count and percentages)
3. Table for newly occurring on-treatment grades 3 or 4 (frequency count and percentages)

All laboratory assessments (including hematology/biochemistry/coagulation without CTC grades, urinalysis, thyroid function, cytokines, pregnancy, and virology) will be listed and those collected outside the on-treatment period will be flagged in the listings.

2.8.3.1 Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST).

The number (%) of subjects with worst post-baseline values will be summarized for the following:

1. ALT or AST > 3xULN
2. ALT or AST > 5xULN
3. ALT or AST > 8xULN
4. ALT or AST > 10xULN
5. ALT or AST > 20xULN
6. TBIL > 2xULN
7. TBIL > 3xULN

8. ALP>1.5xULN
9. ALP>2.0xULN
10. Hy's Law:ALT or AST > 3xULN & TBIL > 2xULN & ALP<2xULN

2.8.4 Other safety data

Other safety data (ECG, vital signs, ECOG performance status, chest X-ray) will be listed.

2.8.4.1 ECG and cardiac imaging data

A standard 12-lead ECGs including PR, QRS, QT, QTcF, QTcB, and HR intervals will be obtained for each subject during the study. The ECGs on C1D1, C2D1, C3D1, C4D1, C5D1 and C6D1 must be performed in triplicate.
The number and percentage of patients with notable ECG values will be presented. The denominator to calculate percentages for each category is the number of patients with both a baseline and a post-baseline evaluation. A newly occurring post-baseline ECG notable value is defined as a post-baseline value that meets the criterion at post-baseline but did not meet the criterion at baseline.

Notable ECG values are defined as:

QT and QTcF
1. New value of > 450 and ⩽ 480 ms
2. New value of > 480 and ⩽ 500 ms
3. New value of > 500 ms
4. Increase from baseline of > 30 ms to ⩽ 60 ms
5. Increase from baseline of > 60 ms

HR
6. Increase from baseline > 25 % and to a value > 100 bpm
7. Decrease from baseline > 25 % and to a value < 50 bpm

PR
8. Increase from baseline > 25 % and to a value > 200 ms
9. New value of > 200 ms
10. QRSIncrease from baseline > 25 % and to a value > 120 ms
11. New values of QRS > 120 ms

All ECG measurements will be listed and those collected outside the on-treatment period will be flagged in the listings. Notable values will be flagged in the listings. Qualitative ECG findings will be listed as well.

2.8.4.2 Vital signs

The number and percentage of patients with notable vital sign values (high/low/high and low) will be presented. The denominator to calculate percentages for each category is the number of patients with both a baseline and a post-baseline evaluation.

Notable vital sign values are defined as:

Systolic blood pressure

1. High: ≥180 mmHg with increase from baseline of ≥20mmHg
2. Low: ≤ 90 mmHg with decrease from baseline of ≥20 mmHg

Diastolic blood pressure

3. High: ≥105 mmHg with increase from baseline of ≥15 mmHg
4. Low: ≤50 mmHg with decrease from baseline of ≥15 mmHg

Pulse rate

5. High: ≥100 bpm with increase from baseline of ≥25 bpm
6. Low: ≤50 bpm with decrease from baseline of ≥25 bpm

Weight

7. High: Increase from baseline of ≥10 %
8. Low: Decrease from baseline of ≥10 %

Body temperature

9. High: ≥39.0 °C
10. Low: ≤ 35.0 °C

All vital sign values will be listed and those collected outside the on-treatment period will be flagged in the listings. Notable values will be flagged in the listings.

2.8.4.3 ECOG performance status

ECOG performance status will be summarized and listed by visit based safety set.

2.8.5 Cardiac Imaging (MUGA/ECHO)

For cardiac imaging descriptive statistics at baseline and at each post -baseline time(if available) will be summarized and listed.

2.9 Pharmacokinetic endpoints

Not Applicable

2.10 PD and PK/PD analyses

Not Applicable

2.11 Patient-reported outcomes

Not Applicable

2.12 Biomarkers

Not Applicable

2.13 Other Exploratory analyses

Not Applicable

2.14 Interim analysis

Scheduled interim data reviews will occur for the primary endpoint of clinical benefit rate only as required by the Bayesian Hierarchical design. The first interim data review will be performed after the 5 subjects have CBR data available within a cohort. Interim analyses will continue every 3 months thereafter provided at least 10 subjects contribute new CBR data to the subsequent interim. At each interim analysis, the tumor cohorts will be evaluated for early futility and early success by comparing posterior quantities for the response rate to pre-specified early stopping criteria.

There is no plan for a formal interim analysis of safety or other secondary endpoints for this study. However, for publication or other purposes, interim data review of clean data will be performed as necessary. At these interim reviews, patient demographics/baseline characteristics, the primary and secondary endpoints as applicable, and all important safety endpoints will be summarized. No formal report will be issued for these data reviews.

3 Sample size calculation

The sample size was chosen by the usual criteria of obtaining adequate power for the alternative hypothesis of interest as given in Sections 6.2.2 and 6.2.3 of Appendix 4 of protocol. This hypothesis corresponds to a generally effective treatment across cohorts and incorporates variation in treatment effects to reflect the realistic expectation that treatment effects may differ by cohort.In this setting, analytical power calculations are not possible, but the design was simulated to obtain the power of the study as shown in the appendix. The sample sizes shown (minimum of 5 for futility stopping, minimum of 10 for early success and maximum of 24 as a cohort cap) achieve adequate power for the alternative hypothesis. The simulations included the expected variable accrual by simulating a Poisson process with expected accrual also shown in the appendix.

4 Change to protocol specified analyses

As per study team suggestion, the definitions of full analysis set (FAS) and safety set have been changed(defined in section 2.2).

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule 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 is considered as on-going: The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 1 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:

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 and ConMeds date imputation

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

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then

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

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	**Rule** (*=last treatment date plus 150 days not > (death date, cut-off date,withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.1.2.1 Prior therapies date imputation

Not Applicable.

5.1.2.2 Post therapies date imputation

Not Applicable.

5.1.2.3 Other imputations

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

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

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 v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 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.

5.4 Statistical models

5.4.1 Primary analysis

The primary efficacy variable, clinical benefit rate, will be analyzed by a Novartis designated Contract Research Organization (CRO), [redacted]. Analysis details are provided in Appendix 4 of the protocol, which is also included in Section 2.5 of this Statistical Analysis Plan.

5.4.2 Secondary analysis

Analysis of binary data

No formal hypothesis testing will be performed. Responses will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper and Pearson 1934].

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – 0.05)) two-sided Pearson-Clopper CI.

Analysis of time to events data

Kaplan-Meier estimates

An estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Kaplan-Meier estimates of the survival function with 95% confidence intervals (Brookmeyer and Crowley 1982) at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties.

6 Reference

Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time, Biometrics 38, 29 - 41.

Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26, 404-413.